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Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria producing extended-spectrum beta-lactamases: a systematic review and meta-analysis

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3 **Variation of effect estimates in the analysis of mortality and length of hospital stay in**
4 **patients with infections caused by bacteria producing extended-spectrum beta-**
5 **lactamases: a systematic review and meta-analysis**
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ABSTRACT

Objective To assess the variation of effect estimates in the analysis of mortality and length of stay (LOS) in patients with infections caused by extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae.

Design Systematic review and meta-analysis

Methods Literature search for clinical studies from 1 January 1960 to 1 October 2018 was conducted in PubMed. Primary outcomes were risk ratios (RRs) of all-cause and attributable mortality and weighted mean differences (WMDs) in LOS in patients with bloodstream infections (BSIs) and non-invasive infections. Any change in the effect estimates was assessed by grouping studies according to design, setting, economy-based country classification, reporting period, microbiological aetiology, infection type, and adjustment for appropriateness of empirical treatment. The impact of ESBL production was calculated using random effect meta-analysis and heterogeneity was evaluated by I^2 statistics.

Results Eighty-four studies including 22,030 patients and 149 outcome measures were included in the meta-analysis. Most studies were retrospective cohorts from high-income countries, providing unadjusted estimates. ESBL production in patients with BSIs (56 studies) increased the RR for all-cause mortality by a factor of 1.70 (95% CI: 1.52-1.90; $p < 0.001$), attributable mortality (16 studies) by 1.75 (95% CI: 1.448-2.108; $p < 0.001$), and WMD in the intensive care unit by 3.07 days (95% CI: 1.61-4.54; $p < 0.001$). WMD in hospital LOS was significantly higher in BSIs (4.41 days; 95% CI: 3.37-5.46; $p < 0.001$) and non-invasive infections (2.19 days; 95% CI: 1.56-2.81; $p < 0.001$). Subgroup analyses showed variation of estimates by study design, population, strain, and assessment of appropriateness of empiric treatment. High heterogeneity was observed in all analyses.

Conclusions Current evidence of the clinical burden of infections caused by ESBL-producing bacteria is highly heterogeneous and based mainly on unadjusted estimates derived from retrospective studies. Despite these limitations, ESBL production in strains causing BSIs seems associated with higher all-cause and attributable mortality and longer hospitalisation.

KEYWORDS

Extended-spectrum beta-lactamase, mortality, bloodstream infection, length of stay, meta-analysis, systematic review

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ▶ Evidence of the impact of ESBL production on mortality and length of stay in strains causing invasive and non-invasive infections was collected systematically.
- ▶ Effect of multiple epidemiological and clinical variables was assessed in the calculation of estimates.
- ▶ Heterogeneity among studies was assessed.
- ▶ Only few studies had been performed in high-risk populations or low-income countries.

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INTRODUCTION

Infections caused by extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae are responsible for high morbidity and mortality worldwide.^{1,2,3} The 2018 World Health Organization list of antibiotic-resistant pathogens identified mortality as the most important criteria to prioritise bacteria for research and development of new, effective antibiotics.¹ In this prioritisation exercise, ESBL-producing Enterobacteriaceae were designated a critical priority because of their high all-cause mortality and high prevalence globally in healthcare-associated and community-acquired infections. The incidence and attributable mortality of multidrug-resistant bacterial infections, including ESBL-producing Enterobacteriaceae, in European countries has been recently estimated using a modelling analysis.⁴ In 2015 ESBL-producing *Escherichia coli* was responsible for almost 300,000 infections in Europe and 9,000 attributable deaths, and ESBL-producing *Klebsiella pneumoniae* caused around 70,000 infections and more than 3,500 deaths. The major limitation of this analysis is the sparseness of evidence on mortality due to ESBL-producing bacteria, which was limited largely to studies conducted in high-income countries.

Two systematic reviews have been performed to define the impact of ESBL production on mortality due to Enterobacteriaceae.^{2,3} Both meta-analyses included studies targeting bloodstream infections (BSIs) and showed doubling all-cause mortality for ESBL-associated bacteraemia compared to non-ESBL Enterobacteriaceae bacteraemia. A major drawback of the analyses, highlighted by the authors, was the lack of control for confounding and limited adjustment for empiric therapy. No systematic review has been performed to assess attributable mortality and other indicators of clinical impact such as length of stay (LOS).

Because estimates of clinical burden drive policy design for antibiotic stewardship and infection control interventions, precise and current estimates are essential. The objective of this systematic review and meta-analysis was to assess the variation of effect estimates in the analysis of mortality and LOS in patients with infections due to ESBL-producing Enterobacteriaceae.

METHODS

Literature search strategy

The search was performed by 2 researchers (BPG and PS) in PubMed on 05 October 2018 using the following search string: (ESBL AND *Escherichia coli* AND mortality) OR (ESBL AND *Klebsiella pneumoniae* AND mortality) OR (ESBL AND *Escherichia coli* AND length

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3 of stay OR length of hospitalisation) OR (ESBL AND *Klebsiella pneumoniae* AND length of
4 stay OR length of hospitalisation). Reference lists of retrieved articles were also searched.

7 **Eligibility criteria**

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9 We included all clinical studies with a comparison group assessing all-cause mortality,
10 attributable mortality, and overall LOS and intensive care unit stay (ICU) LOS in hospitalised
11 patients with ESBL infections. Studies published from 1 January 1960 to 1 October 2018
12 irrespective of the clinical setting and study design were included. The search was restricted
13 to English language publications. Diagnostic studies, reviews, case reports, non-clinical
14 studies, and abstracts of conference presentations were not included.

20 **Data extraction**

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22 Two reviewers (PS and BPG) independently assessed the eligibility of trials and extracted
23 data. In case of disagreement, a third reviewer (DL) was consulted. Extracted data were
24 collected in an electronic worksheet, using EpiInfo 7.1: authors, journal, country, year of
25 publication, year of study, time of data collection, study design, comparison group, study
26 setting, population, aetiology, type and site of infection, and raw data related to mortality and
27 LOS/ICU-LOS. Countries were classified as high-, middle-, or low-income using the World
28 Bank Atlas method.⁵ Adjusted effect estimates such as odds ratios (ORs) or hazard ratios and
29 quality indicators such as reporting of antibiotic therapy, appropriateness of empirical
30 treatment, resistance mechanisms, and minimum inhibitory concentrations (MICs) were also
31 extracted.

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33 Mortality data were extracted as all-cause mortality or attributable mortality as defined in the
34 studies. Where available, prespecified time periods for mortality assessment (i.e., 14 days, 28
35 days, in-hospital) were also extracted. LOS and ICU-LOS were extracted as days with mean
36 and standard deviation or median and interquartile range.

47 **Data analysis**

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49 The primary outcomes for the clinical impact of ESBL infections were RRs of all-cause and
50 attributable mortality and the weighted mean difference (WMD) in LOS and ICU-LOS in
51 patients with ESBL infections compared with those in patients with non-ESBL infections and,
52 where available, with uninfected patients. The impact of ESBL production on attributable and
53 all-cause mortality was calculated with random effect meta-analysis and expressed as RR with
54 95% confidence interval (CI). WMD in days with 95% CI was calculated to express the
55 excess in LOS and ICU-LOS. Analysis of mortality focused on BSIs while LOS was
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determined for BSIs and non-invasive infections (i.e., urinary tract infections, respiratory tract infections, surgical site infection).

Variation of the effect estimate was assessed by grouping the studies according to the following confounders: mortality time assessment (7 vs 14 days), aetiology (*E. coli* vs *K. pneumoniae*), clinical setting (paediatric, oncology, ICU), economic country areas (high-income countries [HICs] vs low- and medium-income countries [LMICs]), study design, assessment of empiric therapy, and year. Subgroup analysis was computed only if more than 2 studies were available for each group. Heterogeneity was evaluated by using I^2 statistics. Overall significance testing was carried out using Wald tests adjusted using the Bonferroni correction. The unadjusted ORs were compared with the adjusted ORs to estimate the effect of adjustment. Reporting and publication bias was presented in funnel plots (supplementary and tested by Egger's test. Statistical analyses were performed using Stata version 15. All meta-analyses were performed in accordance with the Cochrane Collaboration recommendations⁶ and reported according to the PRISMA statement.⁷

The protocol is available online .

(https://im1-tuebingen.de/wp-content/uploads/2019/03/ClinicalImpactAMR_SR_studyprotocol_2018.pdf)

Patient and Public Involvement

There was no patient or public involvement in this systematic review of published literature.

RESULTS

Our literature search identified 1006 studies, and 92 (9.2%) met the eligibility criteria on the basis of abstract screening. Full-text screening excluded an additional 5 articles, providing an evidence base of 87 studies (Figure 1).⁸⁻⁹⁴ The 87 studies included in the qualitative analysis were conducted between 1991 and 2017 in 25 countries, mainly in South Korea (14 studies), Thailand (7), USA (7), Taiwan (7), and Spain (7). Sixty (68.9%) studies were performed in HICs, 26 (29.9%) in LMICs, and 1 included both HICs and LMICs.⁵⁴ About half (44, 50.6%) were retrospective cohort studies, 24 (27.6%) case cohort studies, and 18 (20.7%) prospective cohort studies; 1 study had an interventional design.⁵⁵ The comparison group was patients with infections caused by gram-negative non-ESBL producers in 82 (94.3%) studies, non-infected patients in 2 (2.3%), and both control groups in 3 (3.5%). Most (57, 65.5%) studies included data from the entire hospital, while a few focused on specific settings, mainly ICUs (9, 10.3%) and paediatric wards (8, 9.2%). The most common ESBL-producing bacteria were

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3 *E. coli* (23, 26.4%) and *K. pneumoniae* (17, 19.5%). An overview of study characteristics is
4 provided in online supplementary table S1.

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7 Because data in 3 studies^{20,59,85} were insufficient for quantitative analysis, 84 (96.6%) studies
8 were included in the meta-analysis analysing data from 22,030 patients and 149 outcome
9 measures. Fifty-seven studies analysed BSIs and 10 non-invasive infections. Study
10 characteristics for all studies are provided in online supplementary table S2.

11 **All-cause mortality**

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16 All-cause mortality was reported in 81 studies including 21,942 patients. ESBL production in
17 patients with BSIs increased all-cause mortality by a factor of 1.70 (95% CI: 1.52-1.90;
18 $p<0.001$; $I^2=45.3\%$). The RR increased over time from 1.56 (95% CI: 1.15-2.11; $p=0.004$) in
19 1991-1999 to 1.74 (95% CI: 1.50-2.01; $p<0.001$) in 2000-2009, and it was stable in 2010-
20 2018 (1.72, 95% CI: 1.39-2.13; $p<0.001$). The RR was higher in studies assessing
21 appropriateness of empiric therapy (RR=1.75; 95% CI 1.54-1.99; $p<0.001$) than in those that
22 did not (RR=1.55; 95% CI 1.26-1.90; $p<0.001$). The subgroup analysis by pathogen showed
23 that ESBL production increased the RR in BSIs due to *E. coli* (RR=1.82; 95% CI: 1.50-2.21;
24 $p<0.001$) compared to those due to *K. pneumoniae* (RR=1.48; 95% CI: 1.17-1.87; $p=0.001$).
25 Stratification by population age showed an higher RR in paediatric population (RR=2.09;
26 95% CI: 1.62-2.71; $p<0.001$). Effect estimates did not vary significantly by study country,
27 mortality time assessment (14 vs 28 days), ESBL molecular resistance mechanisms, or study
28 design (Figure 2 and online supplementary figure S1). Adjusted estimates for inappropriate
29 empirical antibiotic therapy were provided for 14 studies. The pooled unadjusted OR for all-
30 cause mortality was 2.91 (95% CI: 2.23-3.81; $p<0.001$, $I^2=27.1\%$; $p=0.164$) and the pooled
31 OR after adjusting for receipt of appropriate empirical treatment was 3.22 (95% CI: 1.53-
32 6.76; $p=0.002$; $I^2=87.5\%$; $p<0.001$).

33 **Attributable mortality**

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Attributable mortality was analysed in 16 studies including 2,885 patients. All studies were
performed in HICs. ESBL production in patients with BSIs increased the risk of attributable
mortality by a factor of 1.75 (95% CI: 1.45-2.11; $p<0.001$; $I^2=0\%$). The RR increased over
time from 1.53 (95% CI: 1.10-2.12; $p=0.011$) in 1991-1999 to 1.91 (95% CI: 1.43-2.54;
 $p<0.001$) in 2000-2009 (Figure 3). Pathogen-specific RR for attributable mortality was 1.60
(95% CI: 1.18-2.15; $p=0.002$) for *K. pneumoniae* and 1.76 (95% CI: 1.33-2.34; $p<0.001$)
when the gram-negative organisms were analysed all together without species differentiation.

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3 The subgroup analysis showed the RR was lower in case cohort studies (1.56; 95% CI: 1.09-
4 2.25; $p=0.016$) than in cohort studies (1.80; 95% CI: 1.37-2.37; $p<0.001$).
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7 **Length of stay**

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9 LOS data were provided in 37 studies (17 on BSIs and 8 on non-invasive infections)
10 analysing 38 outcome measures. The WMD of LOS in patients with BSIs was 4.41 days (95%
11 CI: 3.37-5.46; $p<0.001$) and decreased from 5.72 days (95% CI: 2.69-8.75; $p<0.001$) in 1991-
12 1999 to 4.22 days (95% CI: 3.02-5.43; $p<0.001$) in 2000-2009 and was stable up to 2018
13 (4.30 days; 95% CI: 1.38-7.22; $p=0.004$). Higher WMD ($p<0.001$) was observed for BSIs due
14 to *K. pneumoniae* (7.67 days; 4.63-10.71) than for those due to *E. coli* (6.07 days; 95% CI
15 3.71-8.43). Retrospective cohort studies reported higher ($p<0.001$) WMD (6.43 days; 95% CI:
16 4.66-8.21; $p<0.001$) than case cohort studies (3.32 days; 95% CI: 2.03-4.61). Studies in HICs
17 showed higher WMD (4.56 days; 95% CI 3.43-5.70; $p<0.001$) than studies in LMICs (3.55
18 days; 95% CI 0.84-6.26; $p=0.01$) (Figure 4).
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27 Studies with non-invasive infections reported a WMD of 2.19 days (95% CI: 1.56-2.81;
28 $p<0.001$), which decreased from 7.66 (95% CI: 5.83-9.46; $p<0.001$) in 2000-2009 to 1.44
29 (95% CI: 0.77-2.10; $p<0.001$) in 2010-2018 (online supplementary figure S3).
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33 The data on ICU-LOS were provided in 7 studies and showed that BSIs caused by ESBL
34 producers had a WMD of LOS of 3.07 days (95% CI: 1.61-4.54; $p<0.001$).
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37 Egger's test and the funnel plots (online supplementary figure S4 and S5) showed evidence
38 for small study effects ($p<0.001$) and publication bias.
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41 **DISCUSSION**

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43 This systematic review shows that ESBL production has a significant impact on the most
44 relevant patient-related clinical outcomes. In the subgroup analyses, all-cause mortality,
45 attributable mortality, and LOS both in hospital and in ICU were higher for patients with BSIs
46 due to ESBL-producing Enterobacteriaceae than for patients with BSIs due to non-ESBL-
47 producing strains. Non-invasive infections caused by ESBL-producing strains were associated
48 with prolonged LOS. Within the limitation of the low number of studies evaluating specific
49 patient populations, paediatric and cancer patients seemed to suffer a higher impact of ESBL
50 invasive infections than the overall population. Stratifying by pathogen type, the impact of
51 ESBL production was higher for *E. coli* BSIs than for *K. pneumoniae* BSIs. No relevant
52 differences in mortality analysis emerged with stratification by study design or country
53 income level. Impact of ESBL infections on mortality became more evident in more recent
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3 studies. Studies reporting on appropriateness of empirical therapy, ESBL resistance
4 mechanisms, and MICs showed a higher clinical impact of ESBL infections than studies not
5 assessing these variables. In particular, pooled ORs adjusted for inappropriate empirical
6 treatment, showed a remarkably higher OR for mortality in patients with ESBL infections.
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10 Our findings confirm the results of previous systematic reviews. Schwaber et al. performed a
11 systematic review comparing mortality in ESBL BSIs and non-ESBL BSIs in studies
12 published through 2003.² The authors show a pooled RR for all-cause mortality of 1.85 but, in
13 contrast to our study, they combined *E. coli*, *Klebsiella* spp., and *Proteus* spp. in the analysis
14 because of sample size limitations. Rottier et al. analysed studies published through 2010 and
15 adjusting results for inappropriate empirical treatment found an adjusted OR of 1.37.³ Our
16 study, adding more than 50 studies in 17 years to the Rottier systematic review, confirmed the
17 clinical importance of ESBL production to all-cause mortality and for the first time assessed
18 the role of ESBL production on attributable mortality. We addressed relevant confounders
19 through subgroup analyses and found that population, pathogen, and assessment of empiric
20 therapy all had an impact on estimates. Because we believe that appropriate empirical
21 treatment plays a relevant role in invasive infections, we performed a secondary analysis by
22 pooling only adjusted ORs and confirming the significant impact of antibiotic resistance as
23 already shown in a previously published systematic review.⁹⁵ The impact of ESBL production
24 on LOS has been also estimated, assessing BSIs and non-invasive infections separately and
25 confirming the prolongation of hospitalisation.
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29 Our study has some limitations. Although results of the meta-analyses were significant in all
30 the subgroups, we could analyse only a limited number of studies providing information for
31 subgroups such as haematological patients and low-income countries, making generalizability
32 of results less certain for these specific patient populations. Only a few studies reported MIC
33 data or specific ESBL molecular resistant phenotype (i.e., AmpC). Moreover, publication bias
34 was detected in both the main analyses (all-cause mortality and LOS), thus implying the
35 possibility that results from small studies with non-significant results might have been
36 conducted and not published, resulting in a possible overestimation of our results. The non-
37 homogeneous reporting of some relevant data in published literature (e.g., disease severity
38 and underlying comorbidities) may also have affected the precision of the estimate. Patients
39 with ESBL are intrinsically at higher risk of mortality and complications because they are
40 often older, have more comorbidities or higher antibiotic exposure, and are at higher risk of
41 receiving inappropriate empirical treatment.⁹⁶
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3 In summary, our systematic review emphasises the importance of suspicion and confirmation
4 of ESBL production as soon as possible for invasive infections and demonstrates that ESBL
5 production increases the risk of attributable mortality and LOS in both hospital and ICU for
6 invasive and non-invasive infections. Patients with ESBL infections remain at higher risk of
7 mortality and prolonged LOS even after adjustment for empiric inappropriate treatment.
8 Control for other relevant confounders is hindered by the sparseness of published data. Future
9 studies addressing the clinical burden of drug-resistant infections must include ESBL
10 production and should assess both the impact of molecular mechanisms of resistance and
11 effect on specific patient populations such as haematological patients and those in LMIC.
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28 for the decision to submit for publication.
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44 **Patient consent** Not required
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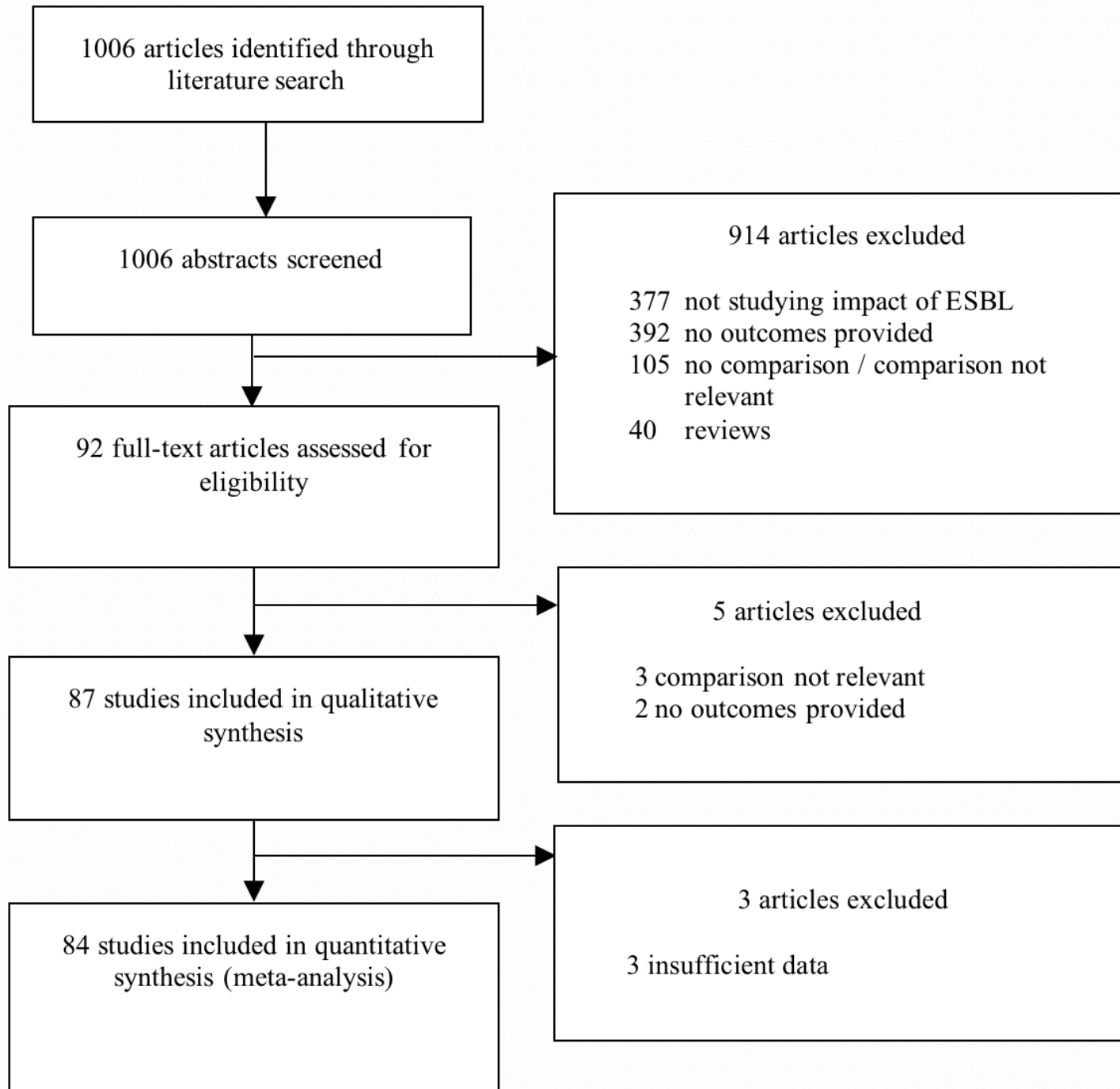
FIGURE LEGENDS

Figure 1: Literature search and study inclusion and exclusion

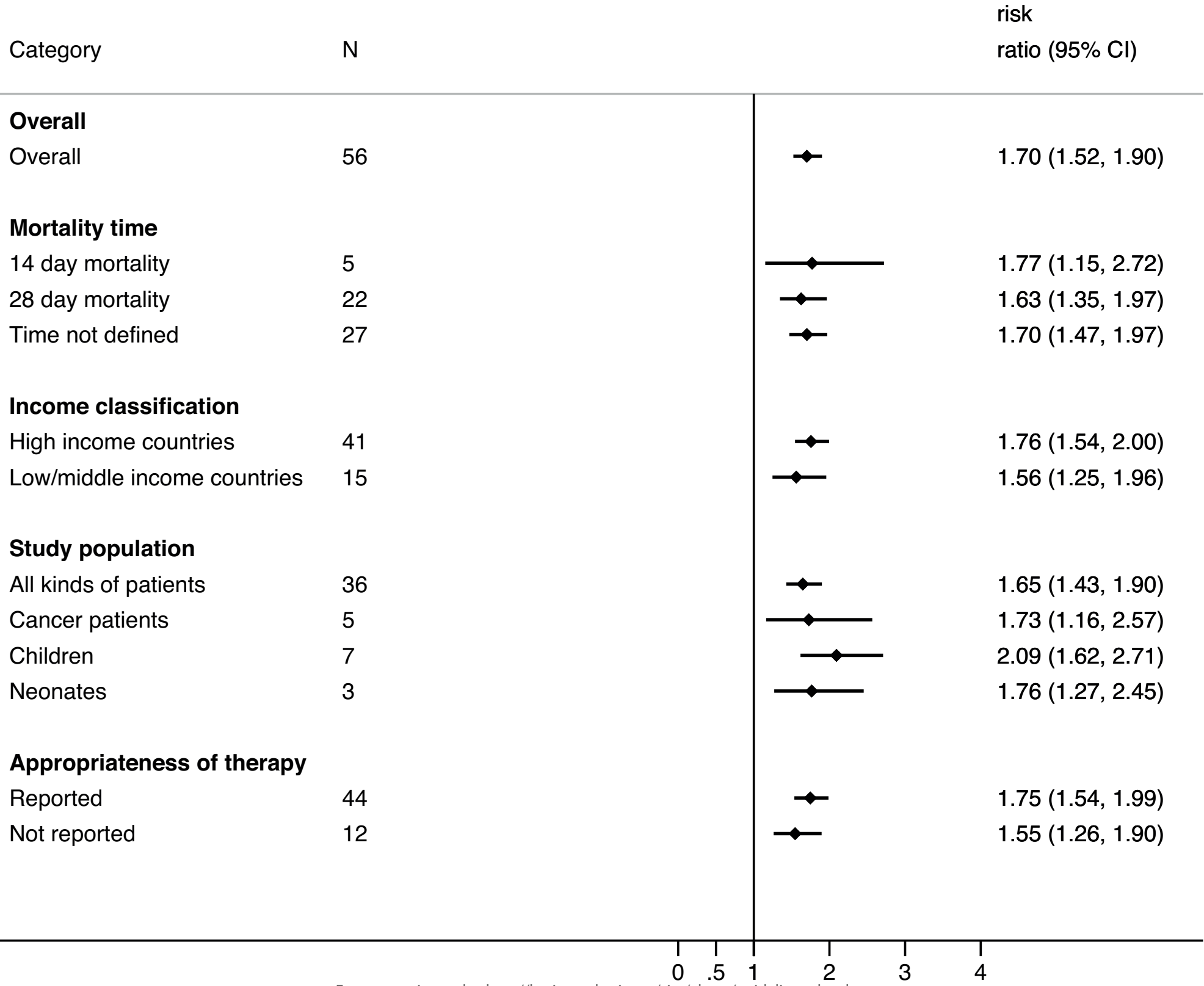
Figure 2: Pooled risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections— subgroups not included in attributable mortality

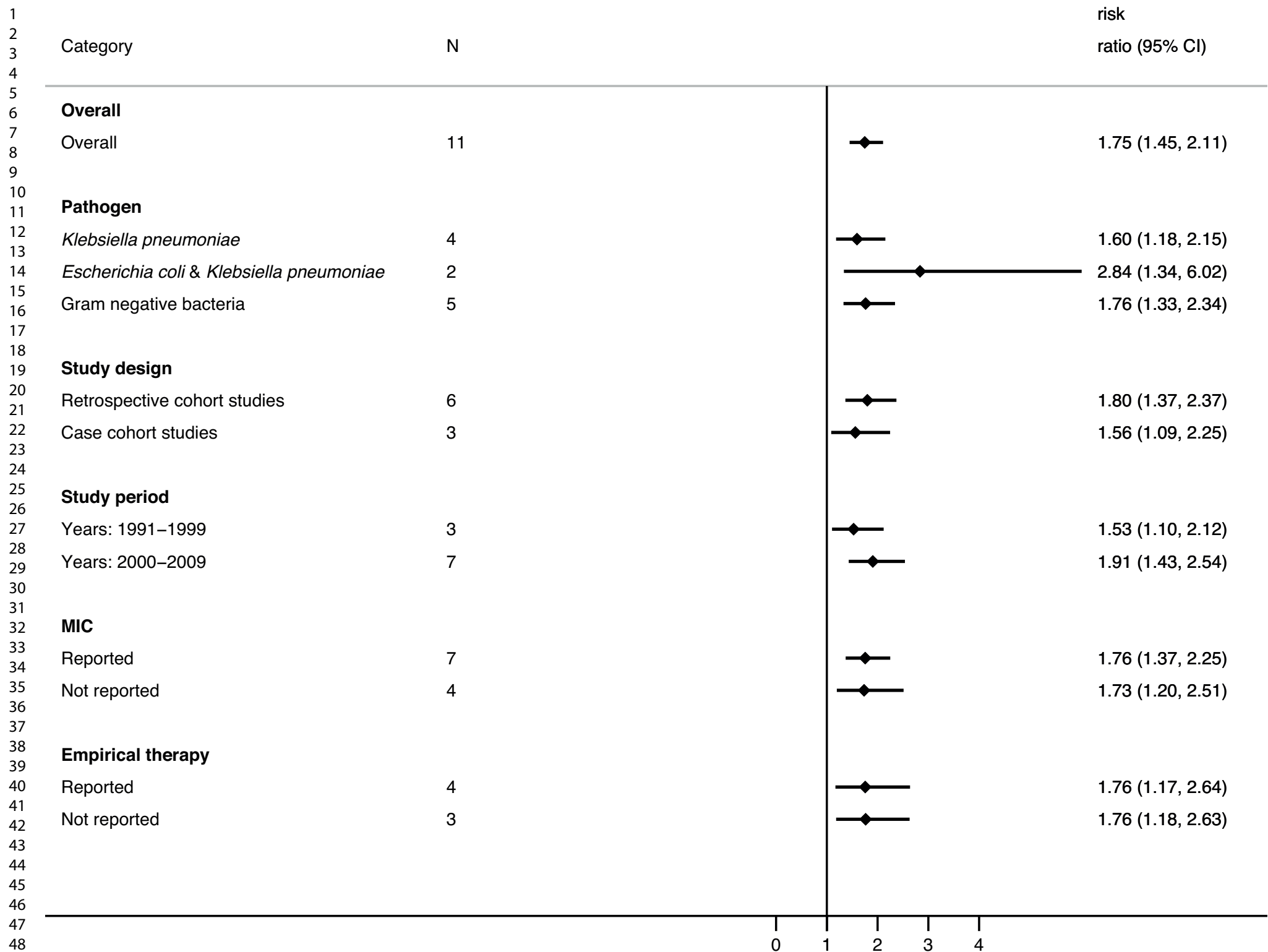
Figure 3: Pooled risk ratios for attributable mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections

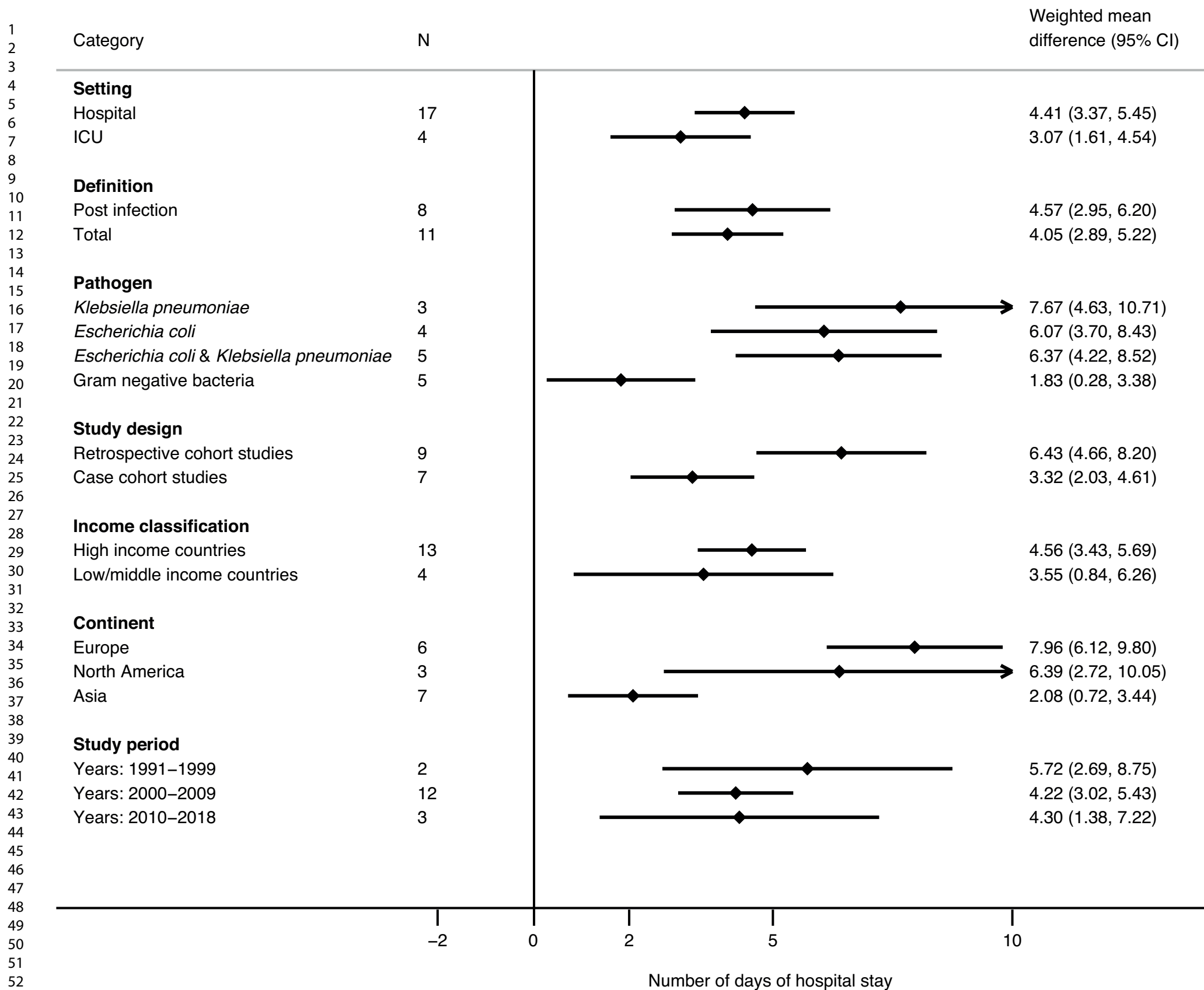
Figure 4: Weighted mean difference in the length of stay for patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections



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Supplementary table S1: Study characteristics overview

Subgroup	All Studies	Bloodstream infections	Noninvasive infections
	87	57	10
Country			
South Korea ^{11,12,14,15,29,33,36,40,42,44,49,50,55,57}	14	9	2
Thailand ^{22,24,43,51-53,86}	7	3	
USA ^{8,16,26,30,46,59,67}	7	2	1
Spain ^{34,38,56,60,68,89,92}	7	4	2
Taiwan ^{10,37,62,69,80,82,94}	7	5	2
China ^{58,71,72,75,85}	5	4	
Israel ^{21,45,90,91}	4	3	
Germany ^{9,39,41,61}	4	3	
Italy ^{23,31,35}	3	3	
Japan ^{74,79,84}	3	3	
Tanzania ^{17,64,73}	3	3	
India ^{47,48,78}	3	1	1
Canada ^{63,65,83}	3	2	
UK ^{20,28,87}	3	3	
France ^{66,77}	2	1	1
South Africa ^{13,81}	2	1	
Brazil ^{13,81}	2	2	
Greece ⁸⁸	1	1	
Hungary ⁹³	1	1	
Lebanon ²⁵	1	-	
Malaysia ²⁷	1	-	1
Mexico ⁷⁰	1	1	
Saudi Arabia ¹⁸	1	1	
Turkey ⁷⁶	1	1	
Continent			
Asia ^{10-12,14,15,18,21,22,23,25,27,29,33,36,37,40,42-45,47-53,55,57,58,62,69,71,72,74,74,78-80,82,84-86,90,91,94}	46	29	6
Europe ^{9,20,23,28,31,34,35,38,39,41,56,60,61,66,68,76,77,87-89,92,93}	22	17	3
North America ^{8,16,26,30,46,59,63,65,67,83}	10	4	1
Africa ^{13,17,64,73,81}	5	4	-
South America ^{19,32,70}	3	3	-
More than 1 continent ⁵⁴	1	-	-

Income group			
High-income countries ^{8-12,14-16,18,20,21,23,26,28-31,34-42,44-46,49,50,55-57,59-63,65-69,74,77,79,80,82-84,87-94,}	60	41	8
Low- and middle-income countries ^{13,17,19,22,24,25,27,32,43,48,51-53,58,64,70-73,75,76,78,81,85,86}	26	16	2
High-income countries AND Low- and middle-income countries ⁵⁴	1	-	-
Study design			
Case cohort study ^{8,10,22-26,29,38,42,44,53,56,59,61-63,65-67,83-85}	24	14	
Retrospective cohort study ^{9,11-15,18,19,21,27,31-36,39-41,43,45,46,48-52,57,58,69,71,72,74-76,79-82,86,87,91,93,94}	44	32	
Prospective cohort study ^{16,17,28,30,37,47,54,60,64,68,70,73,77,78,88-90,92}	18	11	
Year group			
1991-1999 ^{8,58,13,14,15,60,19,23,26,34,44,91,92}	13	10	-
2000-2009 ^{9-12,16-18,20-22,24,25,27-33,35-43,45,47-50,52,53,55,56,59,61,62,65-67,87-90,93,94}	49	31	6
2010-2018 ^{46,51,52,57,63,64,68-86}	25	16	4
Pathogen			
<i>Escherichia coli</i> ^{9,22,28,31,33-35,38,41,43,50,53,56,57,66,68,69,71,74,84,85,89,92}	23	16	3
<i>Klebsiella pneumoniae</i> ^{13,14,18,19,23,27,30,32,39,41,45,59,60,72,76,81,93,94}	17	11	1
<i>E. coli</i> and <i>K. pneumoniae</i> ^{8,11,12,15,24,26,36,41,42,44,46,48,49,52,55,58,61,67,83,86,87}	20	13	2
Gram-negative bacteria ^{10,16,17,20,21,25,29,37,40,47,51,54,62-65,70,73,75,77-80,82,88,90,91}	27	17	4
Study setting			
Entire hospital ^{8,9,14,16,18-25,27,28,31-36,38-44,46-48,50-53,56-58,60,63-67,71,72,74,80,83,84,88-94}	57	40	7
Intensive care unit ^{30,59,62,73,77-79,86,87}	9	5	1
Pediatric ward ^{15,17,26,49,55,76,81,86}	8	7	-
Neonatal ward ^{13,59,62,69,73}	5	3	-
Neonatal intensive care unit ^{59,62,73}	3	2	-
Medical ward ^{11,37,68}	3	-	2
Not provided ^{29,45}	2	-	-
Emergency Department ^{10,82}	2	2	-
Surgical ward ^{30,54}	2	-	-
Burn unit ³⁰	1	-	-
Oncology ⁷⁰	1	1	-
Referral centre for hepatopacreaticobiliary diseases ⁷⁵	1	-	-
Hematological ¹²	1	1	-

Study population			
All kinds of patients ^{8-11,12,16,18-25,27,28,32,33,37-39,41-44,46-48,50-54,56,58,60,61,63-67,74,80,82-84,88,90-93}	55	36	7
Intensive care unit patients ^{30,77-79,85,87}	6	3	1
Children ^{15,17,26,49,55,76,81,86}	8	7	-
Neonates ^{13,59,62,69,73}	5	3	-
Cancer patients ^{31,49,57,70,89}	5	5	-
Immunocompromised patients ⁴⁹	1	1	-
Diabetic patients ⁹⁴	1	1	-
Elderly patients ⁶⁸	1	-	1
Patients with chemotherapy/stem cell transplantation ^{12,89}	2	2	-
Patients after prostatitis biopsy ⁴⁰	1	-	1
Lungs transplantation patients ⁴⁵	1	-	-
Hematological patients ⁷¹	1	1	-
All except cardiothoracic therapy, transplant surgery, burns ⁷²	1	1	
Patients with pyogenic liver abscess ⁷⁵	1	-	-
Data reported			
Treatment information ^{8,10-11,21-24,28-36,38,42-47,49,50,52-63,65,66,68-94}	74	50	6
Appropriateness of treatment ^{8,10-12,14,15,17-19,21-24,28-36,38,42-44,46,47,49,50,52-54,56-58,60-63,65,66,68,70-72,74,75,77,79,81-84,87-94}	62	45	5
Empirical therapy ^{12,14,15,22,23,31,33-36,38,42,49,50,54,56,57,61,74,79,81,92}	22	16	2
Treatment outcome ^{8,10-19,23,24,28-36,38,42-47,49,50,52-55,57-63,65,66,70-72,74,76-79,81-84,86-90,92-94}	64	45	3
Minimum inhibitory concentration results ^{8,9,11,12,14-17,20-23,25,26,30,31,33-39,41,42,45,48-50,52-57,60,61,64,66,67,74-76,78,79,81,83-85,87,92,93}	52	34	4
AmpC genotyping ^{8,9,15,30,39,44,48,54,55,63,64,68,84}	13	6	2

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Supplementary table S2: Characteristics for each study

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Lautenbach E ⁸	1997-1998	USA	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality; LOS	Risk factors for infection with ESBL-producing pathogens, difference in clinical outcomes of infections: resistant vs. susceptible organisms	EC, KP
Kim SH ¹²	2007-2008	South Korea	Cohort study, Retrospective	Non-ESBL-infection	Patients who received either chemotherapy or stem cell transplantation; neutropenic fever	Hematological ward, Others	All-cause mortality (28 day)	Risk factors for acquisition of ESBL, appropriateness of empirical antimicrobial therapy, clinical outcomes in relation to ESBL production	EC, KP
Chayakulkeere M ⁵¹	2015-2015	Thailand	Cohort study, Retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Prevalence & risk factors for infections with & antibiotic susceptibility patterns of & outcomes of patients infected with ESBL-producing-GNB	GNB
Pisarntharak A ⁵²	2003-2007	Thailand	Cohort study, Retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Predictors for mortality associated with community-onset BSI with ESBL-producing pathogens, initial empirical antimicrobial regimens, associated hospital resource utilisation, costs accrued after diagnosis of BSI	EC, KP
Pisarntharak A ⁵³	2003-2004	Thailand	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Mortality associated with community-onset infection due to ESBL-producing pathogens, associated hospital resource use, post-infection hospital cost	EC
Jean SS ⁵⁴	2010-2011	Portugal, Columbia, the Philippines, Taiwan, Thailand	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Surgical ward	Attributable mortality, LOS	Clinical impact on hospitalised patients with community-acquired complicated intra-abdominal infection: ESBL-producing- vs. non-ESBL-producing pathogens	GNB
Lee J ⁵⁵	1999-2005	South Korea	interventional studies	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality (28 day)	impact of a change in antibiotic policy on ESBL-prevalence	EC, KP
Briongos-Figuero A ⁵⁶	2009-2010	Spain	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Characteristics & associated risk factors for EBSL-enterobacteria-UTIs	EC
Ha YE ⁵⁷	2010-2012	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients with cancer	Entire hospital	All-cause mortality (28 day)	Clinical & molecular epidemiology of ESBL-EC bacteraemia, clinical impact of ESBLs on patient outcome	EC
Du B ⁵⁸	1997-1999	China	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors for nosocomial ESBL-EC- and ESBL-KP- bacteraemia & influence on patient outcome.	EC, KP

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Stone PW ⁵⁹	2001	USA	Case cohort study	Non-ESBL-infection	Neonates at NICU	NICU	LOS	costs of interventions aimed at controlling the outbreak, attributable length of stay associated with infection and colonisation with ESBL-KP	KP
Pillay T ¹³	1995-1996	South Africa	Cohort study, retrospective	Non-ESBL-infection	Neonates	Neonatal ward	All-cause mortality	Use of piperacillin/tazobactam in treatment of KP- infection	KP
Kim BN ¹⁴	1999-2000	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, LOS	Prevalence & clinical characteristics of ESBL-KP- bacteraemia, impact of ESBL- production on outcome of patients with KP- bacteraemia in endemic situation.	KP
Kim YK ¹⁵	1993-1998	South Korea	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality	Risk factors & clinical outcomes & clinical responses to treatment of ESBL-EC- and ESBL-KP-bacteraemia, prevalence and types of their ESBLs	EC, KP
Bhavnani SM ¹⁶	2001-2002	USA	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Risk factors for occurrence of invasive ESBL-EC- and ESBL-KP-infections, factors associated with clinical outcome, drug regimens for treatment of infections associated ESBL/non-ESBL strains in real-life clinical practice, clinical response rates for patients treated with cephalosporins/other classes of antimicrobial agents, /carbapenems, clinical response for those patients with infection associated with ESBL and non-ESBL-producing strains with MIC values V8 Ag/mL treated with cephalosporins.	GNB
Blomberg B ¹⁷	2001-2002	Tanzania	Cohort study, prospective	Non-ESBL-infection	Neonates, children	Pediatric ward	All-cause mortality	Prevalence & clinical implications of ESBL production in EC-,KP-, Salmonellae- septicemia	GNB
Pena C ⁶⁰	1993-1995	Spain	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Clinical epidemiology& outcome of ESBL-KP- bacteraemia, relevance of ESBL strains in mortality of patients with hospital-acquired KP-BSI.	KP
Kola A ⁶¹	2002-2004	Germany	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS, ICU-LOS	Outcomes of ESBL-EC- and ESBL-KP-infections	EC, KP
Isai MH ⁶²	2001-2012	Taiwan	Case cohort study	Control group: non-ESBL-infection, second control group: all hospitalised patients	Neonates at NICU	NICU	Attributable mortality, all-cause mortality, LOS	Clinical features& risk factors& molecular epidemiology of ESBL-GNB	GNB
Maslikowska JA ⁶³	2010-2013	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS	Differences in clinical & microbiological outcome, mortality, and/or hospital resource use: ESBL-EC- and ESBL-Ks- vs non-ESBL-EC- and non-ESBL-Ks-infections	GNB

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Onken A ⁶⁴	2012-2013	Tanzania	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Most common bacterial pathogens causing BSI, antimicrobial susceptibility	GNB
Nguyen ML ⁶⁵	2005-2010	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS, ICU-LOS	Risk factors for & patient outcomes associated with ESBL-EC- and ESBL-Ks- bacteraemia, appropriateness of empiric antibiotic therapy & effect of inappropriate empiric therapy on outcomes	GNB
Denis B ⁶⁶	2005-2009	France	Case-control study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day), LOS	Prevalence & risk factors for ESBL-EC bacteraemia, impact on length of stay & 30day mortality	EC
Chopra T ⁶⁷	2004-2009	USA	Case cohort study	Case 2(Control1): non-ESBL-infection, second control group: no infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Predictors of ESBL-EC- and ESBL-KP-BSI, focus on cefepime exposure.	EC, KP
Panhotra BR ¹⁸	2001-2003	Kingdom of Saudi Arabia	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors & clinical outcome of ESBL-KP-bacteraemia (hospital acquired)	KP
Marra AR ¹⁹	1996-2001	Brazil	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	ESBL-KP- associated mortality	KP
Skippen I ²⁰	2003-2005	UK	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors for & outcomes of ESBL-EC- and ESBL-KP-invasive transmission of organism in the healthcare setting	GNB
Schwaber MJ ²¹	2000-2003	Israel	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Outcomes of ESBL-production in Enterobacteriaceae-bacteraemia.	GNB
Apisarnthanarak A ²²	2003-2004	Thailand	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	All adult patients	Entire hospital	All-cause mortality, LOS	Clinical & molecular epidemiologic factors associated with community onset ESBL-EC- infections, hospital resource utilisation, estimate costs associated with medical care (hospitalised patients)	EC
Umbarello M ²³	1999-2003	Italy	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS, ICU-LOS	Factors associated with isolation of ESBL- KP-strains	KP
Zeistner R ⁹	2008-2010	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital,	All-cause mortality, LOS	Difference in mortality: ESBL-EC-BSIs vs. non-ESBL-EC-BSIs, molecular epidemiology of ESBL-positive isolates	EC

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Apisarntharak A ²⁴	2003-2004	Thailand	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Risk factors for & outcomes of ESBL-EC- and ESBL-KP-infections (healthcare associated)	EC, KP
Kanafani ZA ²⁵	2003	Lebanon	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Epidemiology of infections with ESBL-EC and ESBL-Ks at AUBMC risk factors & outcomes of infections - focus on effect of prior antibiotic administration & the risks imparted by specific classes of antimicrobial agents	GNB
Zaoutis TE ²⁶	1999-2003	USA	Case cohort study	Non-ESBL-infection	Children	Entire hospital	All-cause mortality, LOS	Risk factors & outcomes associated with ESBL-EC-and ESBL-KP-BSI	EC, KP
Goh LC ²⁷	2003-2004	Malaysia	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Impact of ESBL-KP-respiratory tract infections on hospital mortality, requirement for mechanical ventilation & length stay	KP
Melzer M ²⁸	2003-2005	UK	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Differences in mortality & length of hospital stay & time from bacteraemia to death in patients with ESBL-EC- vs. non-ESBL-EC-bacteremic-infection	EC
Song KH ²⁹	2000-2006	South Korea	Case cohort study	Non-ESBL-infection	Patients with spontaneous bacterial peritonitis	Not provided	All-cause mortality (28 day)	Outcomes of ESBL-EC-and ESBL-Ks- vs non-ESBL-EC-and ESBL-Ks-SBP (based on isolation from ascites), impact of ineffective initial antimicrobial therapy on outcome in patients with ESBL-EC- and ESBL-Ks-SBP, risk factors for infection by ESBL-producing microorganisms.	GNB
Bennett JW ³⁰	2004-2008	USA	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU, Surgical ward, Burn unit	All-cause mortality (28 day)	ESBL types and strain variability, presence of host factors to determine potential role in morbidity and mortality during ESBL-KP-infections	KP
Recarichi EM ³¹	2000-2007	Italy	Cohort study, retrospective	Non-ESBL-infection	Patients with hematological malignancies	Entire hospital	All-cause mortality (28 day)	Risk factors for mortality in patients suffering from hematological malignancies with concurrent EC-bacteraemia. Focus on impact of ESBL- production & fluoroquinolone resistance by bacterial isolates	EC
Fuon FF ³²	2006-2009	Brazil	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day), LOS	Risk factors & mortality rate in ESBL-KP-bacteraemia	KP
Kang CI ³³	2008-2009	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Risk factors of ESBL-EC among community-onset bacteraemia, treatment outcomes	EC

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Pena C ³⁴	1996-2003	Spain	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Risk factors for mortality among patients with EC- infections	EC
Tumbarello M ³⁵	2006	Italy	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	ICU, Medical ward, Entire hospital, surgical wide	All-cause mortality (21 day), LOS	Clinical & economic impacts of ESBL production, inadequate Initial Antibiotic Therapy of EC-BSI	EC
Kang C ³⁶	2006-2009	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality (28 day)	Impact of ESBL-producing bacteraemia on outcome in patients with hematologic malignancy.	EC, KP
Wu YH ³⁷	2009-2012	Taiwan	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Medical ward	LOS	Host-related risk factors for community-onset UTI due to levofloxacin- or cefazolin-nonsusceptible isolates or uropathogens with ESBL production, clinical impact of UTIs due to antimicrobial-nonsusceptible pathogens	GNB
Rodriguez-Bano J ³⁸	2004-2006	Spain	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Epidemiology & risk factors (focus on previous antimicrobial use) & mortality rate for patients with ESBL-EC-COBSI	EC
Gürtzke S ³⁹	2008-2011	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Distribution of ESBL genotypes, hospital mortality in cases of ESBL-KP-BSI	KP
Oh MM ⁴⁰	2006-2011	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients after Prostatitis Biopsy	Entire hospital	LOS	Impact of ESBL-positive-strains on clinical course & progression to chronic prostatitis in patients with postbiopsy acute prostatitis.	GNB
Leistner R ⁴¹	2008-2011	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Financial disease burden attributable to ESBL-positive species in cases of EC-and KP-BSI	EC, KP
Lin JN ⁴⁰	2005-2009	Taiwan	Case cohort study	Non-ESBL-infection	All kinds of patients	Emergency Room	Attributable mortality, all-cause mortality (28 day), LOS, ICU-LOS	Clinical & microbiological characteristics, risk factors for acquisition of infection, prescription of initial empirical antibiotics mortality rate of infection	GNB
Ku NS ⁴²	2006-2010	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Clinical usefulness of breakpoints for treatment of Enterobacteriaceae-bacteraemia, (focus on EC- and Ks-bacteraemia): CLSI 2009- vs. CLSI 2010-guidelines.	EC, KP

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Anunnatsiri S ⁴³	2005-2006	Thailand	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Incidence of ESBL-EC-septicemia, factors associated with infection & clinical outcomes	EC
Kang CI ⁴⁴	1998-2002	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Hospital-wide	All-cause mortality (28 day)	Risk factors for mortality & treatment outcome of ESBL-EC- and ESBL-KP-BSI	EC, KP
Raviv Y ⁴⁵	2004-2007	Israel	Cohort study, retrospective	Control group: non-ESBL-infection, second control group: no infection	patients with lung transplantation	Not provided	All-cause mortality (28 day)	Outcomes of lung transplant recipients infected by CRKP and ESBL carbapenem-sensitive KP (referred to MDR-KP)	KP
Kim HJ ¹¹	2005-2010	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Medical ward	All-cause mortality (28 day), LOS	Clinical outcome of patients with biliary tract infection: ESBL-producing bacterial isolates vs. non-ESBL-producing-bacterial isolates, predictors of poor prognosis, impact of ineffective antimicrobial therapy on clinical outcome	EC, KP
MacVane SH ⁴⁶	2011-2012	USA	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS	clinical & economic outcomes of patients with ESBL-EC- and ESBL-KP-UTI vs. non-ESBL-EC- and non-ESBL-KP-UTI	EC, KP
Abhilash KP ⁴⁷	2007	India	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Prevalence & risk factors & outcome of antibiotic treatment among hospitalised patients with ESBL-EC- and ESBL-Ks-BSI	GNB
Rhantni M ⁴⁸	2006	India	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Prevalence & impact on clinical outcome of ESBL-production among nosocomial isolates of EC & KP	EC, KP
Han SB ⁴⁹	2009-2013	South Korea	Cohort study, retrospective	Non-ESBL-infection	Children (immunocompromised, with cancer, neutropenic fever)	Pediatric ward	Attributable mortality, all-cause mortality (28 day)	Clinical outcomes of ESBL-EC- and ESBL-KP-bacteraemia & their antibiotic susceptibilities	EC, KP
Lee S ⁵⁰	2009-2011	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients with Acute Pyelonephritis	Entire hospital	All-cause mortality (14 day), LOS	Impact of ESBL on clinical outcomes of Acute Pyelonephritis treated with empirical ceftriaxone (which was inappropriate for ESBL-producing organisms)	EC
Artero A ⁶⁸	2013-2015	Spain	Cohort study, prospective	Non-ESBL-infection	Elderly	Medical ward	All-cause mortality, LOS	Identify clinical factors to predict ESBL-EC among elderly patients with UTI admitted to hospital in a high rate setting of ESBL-EC	EC

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Chen IL ⁶⁹	2004-2015	Taiwan	Cohort study, retrospective	Non-ESBL-infection	Neonates	Neonatal ward	All-cause mortality	Compare the clinical characteristics & laboratory data of preterm babies with EC BSI: survival vs. nonsurvival groups, ESBL vs non-ESBL groups, determine the predictive factors of EC BSI in preterm babies	EC
Islas-Munoz B ⁷⁰	2016-2017	Mexico	Cohort study, prospective	Non-ESBL-infection	Cancer patients	Oncological ward	All-cause mortality (28 day)	Evaluate the clinical epidemiological characteristics & risk factors associated with mortality in cancer patients with BSI-special emphasis on MDR bacteria	GNB (and others)
Ma J ⁷¹	2012-2015		Cohort study, retrospective	Non-ESBL-infection	Patients with hematological diseases	Entire hospital	All-cause mortality (28 day)	Evaluate the antimicrobial resistance & clinical features & risk factors for septic shock & death of nosocomial EC-BSI	EC
Man MY ⁷²	2009-2016	China	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients, except patients from Burn unit, transplant surgery ward or with thoracic therapy	Entire hospital	All-cause mortality (28 day)	Evaluate the incidence & clinical characteristics & outcomes of patients with KP BSI in critical care & general ward settings	KP
Marando R ⁷³	2016	Tanzania	Cohort study, prospective	Non-ESBL-infection	Neonates	NICU	All-cause mortality	Investigate factors associated with ESBL-PE neonatal sepsis & mortality among neonates, characterise selected isolates to show virulence potential & transmission dynamics	GNB
Namikawa H ⁷⁴	2011-2015	Japan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Investigate clinical characteristics of patients with ESBL-EC-BSI	EC
Shi SH ⁷⁵	2008-2015	China	Cohort study, retrospective	Non-ESBL-infection	Patients with pyogenic liver abscess	Centre for hepatopancreaticobiliary diseases	All-cause mortality, LOS	Aetiology & morbidity & clinical characteristics of pyogenic liver abscess caused by ESBL-PE	GN
Tanir Basaranoglu S ⁷⁶	2011-2015	Turkey	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality (28 day)	Assess risk factors for health care associated ESBL-KP-BSI in children, analyze clinical outcomes: ESBL-KP vs. non-ESBL-KP	KP
Bazazi K ⁷⁷	2009-2015	France	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality, LOS, ICU-LOS	Determine, among ESBL-PE carriers, the prevalence & associated factors & clinical impact of ESBL-PE pneumonia, determine factors associated with ICUAP caused by carbapenem-resistant bacteria	GNB

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Ray S ⁷⁸	2014-2016	India	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Investigate spectrum of microbial resistance pattern in the community and their effects on mortality	GNB
Haruki Y ⁷⁹	2006-2016	Japan	Cohort study, retrospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Compare the clinical characteristics & outcomes of critically ill patients in an ICU, who were hospitalised for BSI caused by ESBL-EC or non-ESBL-EC.	GNB
Lin WT ⁸⁰	2009-2014	Taiwan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Investigate the clinical manifestations & bacteriological features of culture-proven, GNB arthritis	GNB
Guys H ⁸¹	2006-2011	South Africa	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality	Describe the clinical presentation of KPBSI, risk factors associated with ESBL-KPBSI, antibiotic susceptibility patterns of the KP isolates & KPBSI mortality including factors associated with in-patient mortality	KP
Lee CC ⁸²	2008-2013	Taiwan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Emergency Department	Attributable mortality, all-cause mortality (28 day), LOS, ICU-LOS	Analyse the impact of ESBL-producing isolates on the outcome of bacteremic patient after controlling for baseline patient characteristics & bacteraemia severity by using a propensity-matched analysis (PSM)	GNB
Huang YY ⁸³	2011-2013	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Determine cumulative incidence of ESBL urosepsis, identify major risk factors for ESBL urosepsis, determine impact of international travel on development of ESBL urosepsis	EC, KP
Komatsu Y ⁸⁴	2008-2013	Japan	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Identify risk factors & clinical outcomes in patients with BSI due to ESBL- or carbapenemase-producing EC, determine prevalence & genetic background	EC
Liu MM ⁸⁵	2011-2016	China	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	ICU-patients	ICU	All-cause mortality	Identify risk factors for ESBL-producing ECBSI among carriers at ICU	EC
Nivesvivat T ⁸⁶	2010-2017	Thailand	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality, LOS	Determine prevalence, risk factors & clinical outcomes of ESBL-producing EB in paediatric BSI	EC, KP

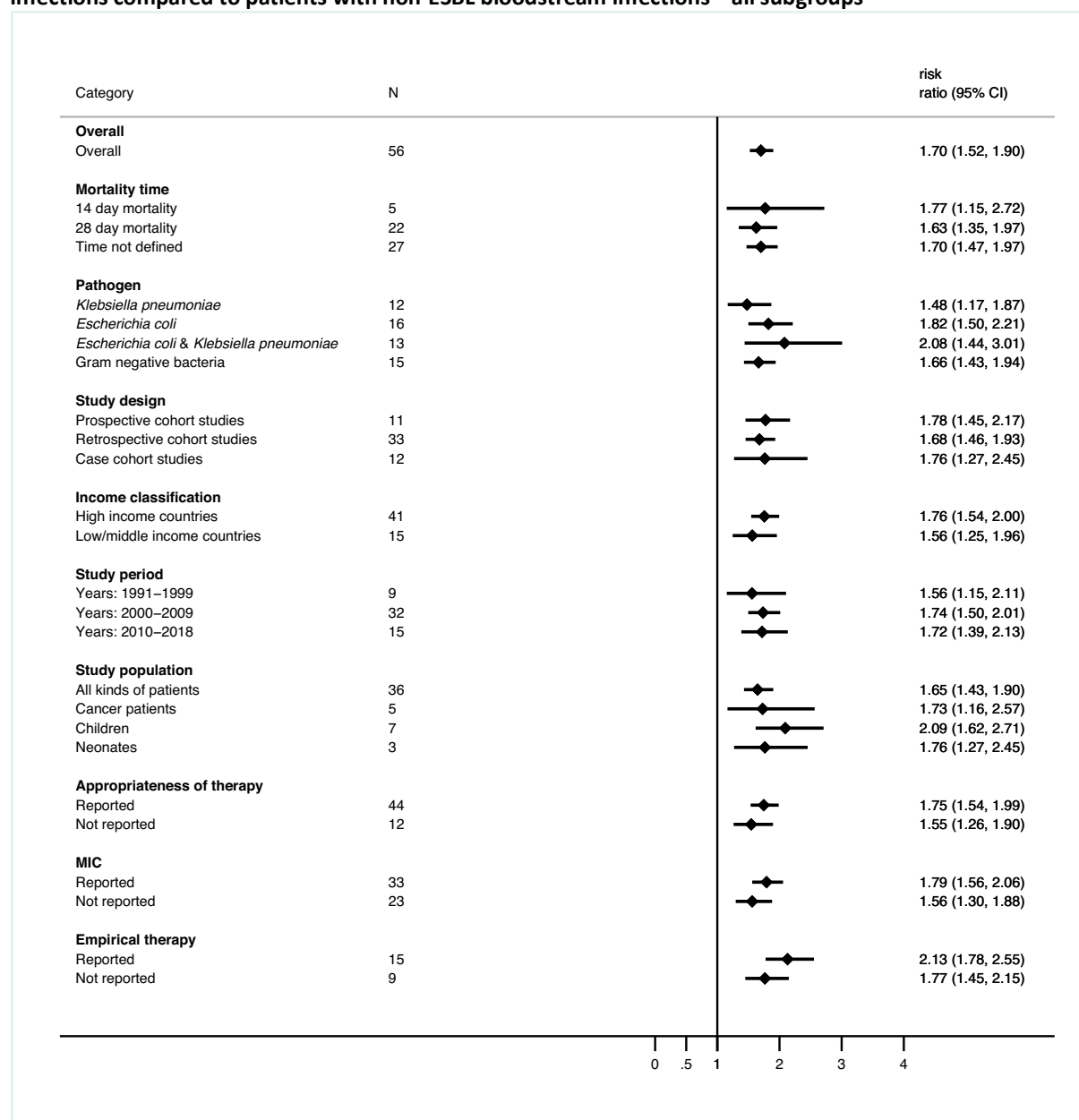
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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Cordery RJ ⁸⁷	2004-2006	UK	Cohort study, retrospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Elucidate specific risk factors for the acquisition of ESBL infection in the ICU; all-cause mortality (in ICU) compared in patients with infections due to ESBL- and non-ESBL-producing organisms	GNB
Paikos GL ⁸⁸	2003-2005	Greece	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Identify risk factors associated BSI caused by integron-carrying EB; evaluate the consequences of these genetic elements on patient outcome	GNB
Gudiol C ⁸⁹	2006-2008	Spain	Cohort study, prospective	Non-ESBL-infection	Cancer patients and hematopoietic stem cell transplant patients	Entire hospital	All-cause mortality	Assess clinical features, risk factors, molecular epidemiology & outcome of ESBLEC BSI in hospitalised cancer patients	EC
Marchaim D ⁹⁰	2006-2008	Israel	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Define predictors & outcomes of ESBL BSI among patients with bacteraemia due to EB upon hospital admission	GNB
Menashe G ⁹¹	1997	Israel	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Determine: prevalence of ESBL-P organisms among adult patients with nosocomial EB BSI treated in our institution; association between ESBL production & resistance to other antibiotics; clinical characteristics of patients with nosocomial ESBL-P BSI compared with those infected with non-producing strains; impact of ESBL production on outcome of patients with nosocomial EB BSI	GNB
Ortega M ⁹²	1991-2007	Spain	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Describe source, resistance rate to fluoroquinolone & beta-lactam antibiotics and mortality of EC BSI episodes in a single institution; identify predictive factors for isolation of fluoroquinolone-resistant or ESBL- producing strains.	EC
Sziglyi M ⁹³	2005-2008	Hungary	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality,	Investigate risk factors for & outcomes of BSI caused by ESBL-producing and ESBL-non-producing KP	KP
Tsai SS ⁹⁴	2005-2006	Taiwan	Cohort study, retrospective	Non-ESBL-infection	Diabetic patients	Entire hospital	All-cause mortality	Analyze characteristics, risk factors & outcomes of diabetic patients with community- vs. hospital-acquired KP BSI	KP

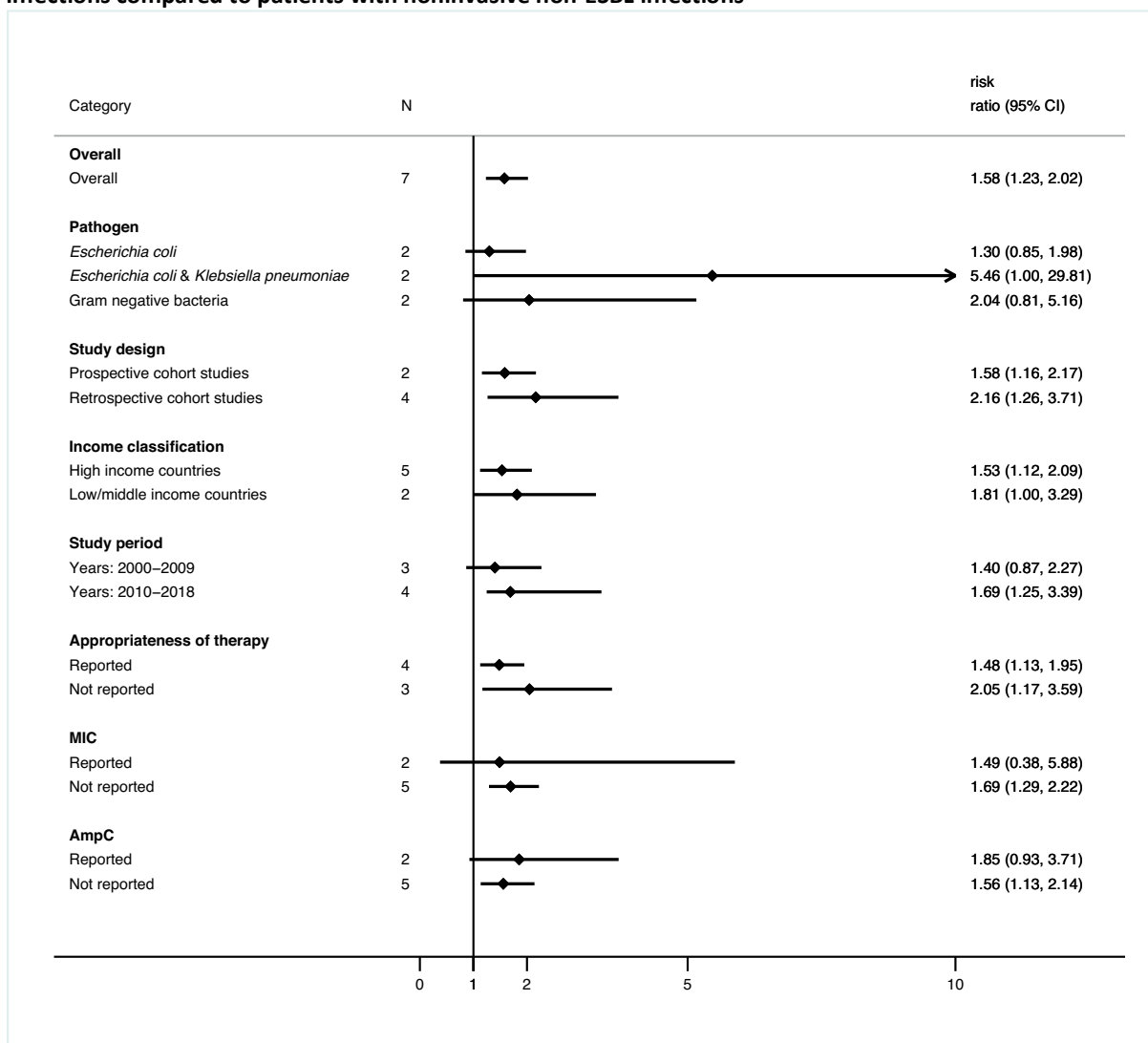
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3 EC = *Escherichia coli*
4 KP = *Klebsiella pneumoniae*
5 GNB = Gram-negative bacteria
6 BSI = Bloodstream infection
7 UTI = Urinary tract infection
8 ICU = Intensive care unit
9 NICU = Neonatal intensive care unit
10 ESBL-PE = Extended-spectrum beta-lactamase-producing Enterobacteriaceae
11 EB = Enterobacteriaceae
12 LOS = Length of stay
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Supplementary figure S1: Pooled risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections—all subgroups

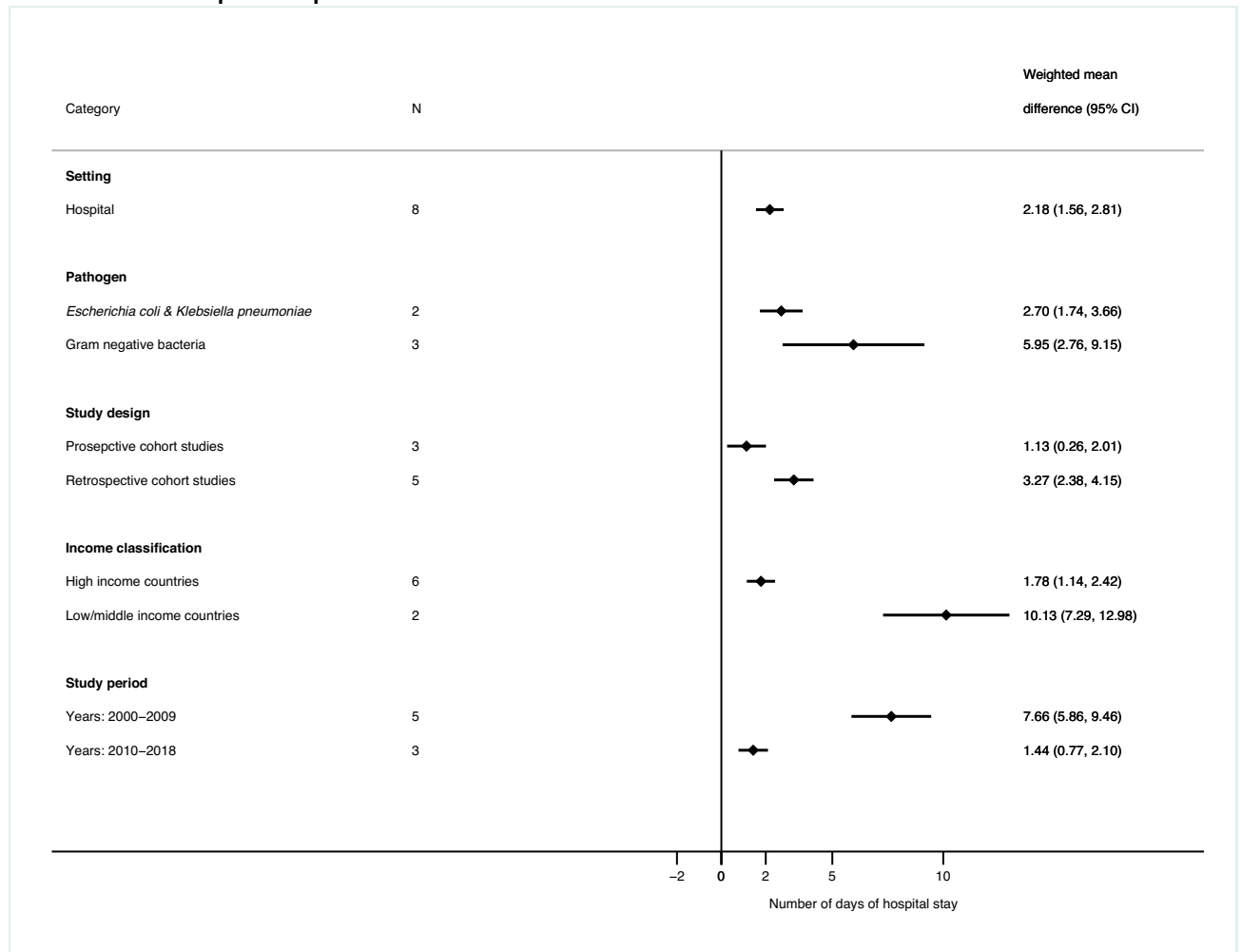


Supplementary figure S2: Pooled risk ratios for all-cause mortality in patients with noninvasive ESBL infections compared to patients with noninvasive non-ESBL infections

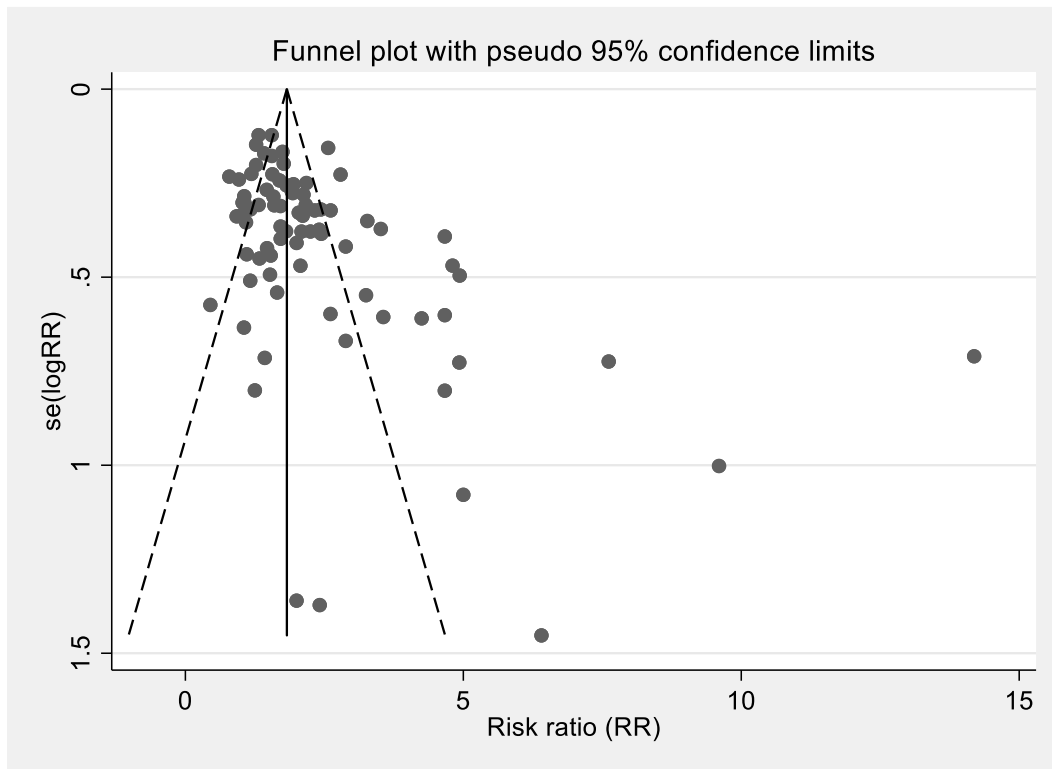


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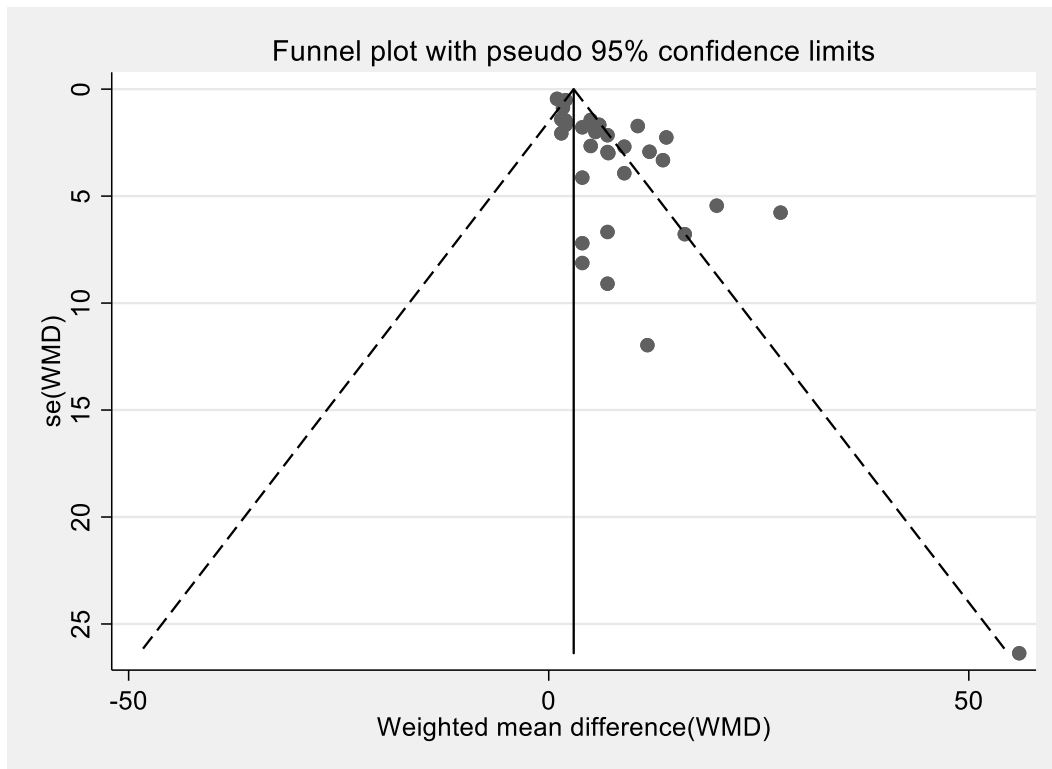
Supplementary figure S3: Weighted mean differences in length of hospital stay in patients with noninvasive ESBL infections compared to patients with noninvasive non-ESBL infections



Supplementary figure S4: Funnel plot of risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections



Supplementary figure S5: Funnel plot of weighted mean differences in the length of stay for patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections





PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	5,6



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	suppl.material
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	21-23 and suppl.material
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7,8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria producing extended-spectrum beta-lactamases: a systematic review and meta-analysis

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Complete List of Authors:	Shamsrizi, Parichehr; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease Gladstone, Beryl Primrose ; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease Carrara, Elena; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health Luise, Dora; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health Cona, Andrea; ASST Santi Paolo e Carlo, Clinic of Infectious and Tropical Diseases, Department of Health Sciences Bovo, Chiara; Integrated University Hospital of Verona, Medical Direction Tacconelli, Evelina; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases, Epidemiology
Keywords:	Extended-spectrum beta-lactamase, mortality, bloodstream infection, length of stay, meta-analysis, systematic review

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3 1 **Variation of effect estimates in the analysis of mortality and length of hospital stay in**
4 **patients with infections caused by bacteria producing extended-spectrum beta-**
5 **lactamases: a systematic review and meta-analysis**
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1 ABSTRACT

2 **Objective** To assess the variation of effect estimates in the analysis of mortality and length of
3 stay (LOS) in patients with infections caused by extended-spectrum beta-lactamase (ESBL)-
4 producing *Enterobacteriaceae*.

5 **Design** Systematic review and meta-analysis

6 **Methods** Literature search for clinical studies from 1 January 1960 to 1 October 2018 was
7 conducted in PubMed. Primary outcomes were risk ratios (RRs) of all-cause and attributable
8 mortality and weighted mean differences (WMDs) in LOS in patients with bloodstream
9 infections (BSIs) and non-invasive infections. Any change in the effect estimates was
10 assessed by grouping studies according to design, setting, economy-based country
11 classification, reporting period, microbiological aetiology, infection type, and adjustment for
12 appropriateness of empirical treatment. The impact of ESBL production was calculated using
13 random effect meta-analysis and heterogeneity was evaluated by I^2 statistics and
14 metaregression.

15 **Results** Eighty-four studies including 22,030 patients and 149 outcome measures were included
16 in the meta-analysis. Most studies were retrospective cohorts from high-income countries,
17 providing unadjusted estimates. ESBL production in patients with BSIs (56 studies) increased
18 the RR for all-cause mortality by a factor of 1.70 (95% CI: 1.52-1.90; $p < 0.001$), attributable
19 mortality (16 studies) by 1.75 (95% CI: 1.448-2.108; $p < 0.001$), and WMD in the intensive care
20 unit by 3.07 days (95% CI: 1.61-4.54; $p < 0.001$). WMD in hospital LOS was significantly higher
21 in BSIs (4.41 days; 95% CI: 3.37-5.46; $p < 0.001$) and non-invasive infections (2.19 days; 95%
22 CI: 1.56-2.81; $p < 0.001$). Subgroup analyses showed variation of estimates by study design,
23 population, strain, and assessment of appropriateness of empiric treatment. High heterogeneity
24 was observed in all analyses.

25 **Conclusions** Current evidence of the clinical burden of infections caused by ESBL-producing
26 bacteria is highly heterogeneous and based mainly on unadjusted estimates derived from
27 retrospective studies. Despite these limitations, ESBL production in strains causing BSIs seems
28 associated with higher all-cause and attributable mortality and longer hospitalisation.

29 KEYWORDS

30 Extended-spectrum beta-lactamase, mortality, bloodstream infection, length of stay, meta-
31 analysis, systematic review
32

1 STRENGTHS AND LIMITATIONS OF THIS STUDY

- 2 ▶ Evidence of the impact of ESBL production on mortality and length of stay in strains
- 3 causing invasive and non-invasive infections was collected systematically.
- 4 ▶ Effect of multiple epidemiological and clinical variables was assessed in the calculation of
- 5 estimates.
- 6 ▶ Heterogeneity among studies was assessed.
- 7 ▶ Only few studies had been performed in high-risk populations or low-income countries.

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1 INTRODUCTION

2 Infections caused by extended-spectrum beta-lactamase (ESBL)-producing
3 *Enterobacteriaceae* are responsible for high morbidity and mortality worldwide.^{1,2,3} The 2018
4 World Health Organization list of antibiotic-resistant pathogens identified mortality as the most
5 important criteria to prioritise bacteria for research and development of new, effective
6 antibiotics.¹ In this prioritisation exercise, ESBL-producing *Enterobacteriaceae* were
7 designated a critical priority because of their high all-cause mortality and high prevalence
8 globally in healthcare-associated and community-acquired infections. The incidence and
9 attributable mortality of multidrug-resistant bacterial infections, including ESBL-producing
10 *Enterobacteriaceae*, in European countries has been recently estimated using a modelling
11 analysis.⁴ In 2015 ESBL-producing *Escherichia coli* was responsible for almost 300,000
12 infections in Europe and 9,000 attributable deaths, and ESBL-producing *Klebsiella pneumoniae*
13 caused around 70,000 infections and more than 3,500 deaths. The major limitation of this
14 analysis is the sparseness of evidence on mortality due to ESBL-producing bacteria, which was
15 limited largely to studies conducted in high-income countries.

16 Two systematic reviews have been performed to define the impact of ESBL production on
17 mortality due to *Enterobacteriaceae*.^{2,3} Both meta-analyses included studies targeting
18 bloodstream infections (BSIs) and showed doubling all-cause mortality for ESBL-associated
19 bacteraemia compared to non-ESBL *Enterobacteriaceae* bacteraemia. A major drawback of the
20 analyses, highlighted by the authors, was the lack of control for confounding and limited
21 adjustment for empiric therapy. No systematic review has been performed to assess attributable
22 mortality and other indicators of clinical impact such as length of stay (LOS).

23 Because estimates of clinical burden drive policy design for antibiotic stewardship and infection
24 control interventions, precise and current estimates are essential. The objective of this
25 systematic review and meta-analysis was to assess the variation of effect estimates in the
26 analysis of mortality and LOS in patients with infections due to ESBL-producing
27 *Enterobacteriaceae*.

28 METHODS

29 Literature search strategy

30 The search was performed by 2 researchers (BPG and PS) in PubMed on 05 October 2018 using
31 search terms (supplementary table S1) relevant to the following combinations: (ESBL AND
32 *Escherichia coli* AND mortality) OR (ESBL AND *Klebsiella pneumoniae* AND mortality) OR
33 (ESBL AND *Escherichia coli* AND length of stay OR length of hospitalisation) OR (ESBL

1 AND *Klebsiella pneumoniae* AND length of stay OR length of hospitalisation). Reference lists
2 of retrieved articles were also searched.

3 **Eligibility criteria**

4 We included all clinical studies with a comparison group assessing all-cause mortality,
5 attributable mortality, and overall LOS and intensive care unit stay (ICU) LOS in hospitalised
6 patients with ESBL infections. Studies published from 1 January 1960 to 1 October 2018
7 irrespective of the clinical setting and study design were included. No language restriction has
8 been applied. Diagnostic studies, reviews, case reports, non-clinical studies, and abstracts of
9 conference presentations were not included.

10 **Data extraction**

11 Two reviewers (PS and BPG) independently assessed the eligibility of trials and extracted data.
12 In case of disagreement, a third reviewer (DL) was consulted. Extracted data were collected in
13 an electronic worksheet, using EpiInfo 7.1: authors, journal, country, year of publication, year
14 of study, time of data collection, study design, comparison group, study setting, population,
15 aetiology, type and site of infection, and raw data related to mortality and LOS/ICU-LOS.
16 Countries were classified as high-, middle-, or low-income using the World Bank Atlas
17 method.⁵ Adjusted effect estimates such as odds ratios (ORs) or hazard ratios and quality
18 indicators such as reporting of antibiotic therapy, appropriateness of empirical treatment,
19 resistance mechanisms, and minimum inhibitory concentrations (MICs) were also extracted.
20 Mortality data were extracted as all-cause mortality or attributable mortality as defined in the
21 studies. Where available, prespecified time periods for mortality assessment (i.e., 14 days, 28
22 days, in-hospital) were also extracted. LOS and ICU-LOS were extracted as days with mean
23 and standard deviation or median and interquartile range.

24 **Data analysis**

25 The primary outcomes for the clinical impact of ESBL infections were RRs of all-cause and
26 attributable mortality and the weighted mean difference (WMD) in LOS and ICU-LOS in
27 patients with ESBL infections compared with those in patients with non-ESBL infections and,
28 where available, with uninfected patients. The impact of ESBL production on attributable and
29 all-cause mortality was calculated with random effect meta-analysis and expressed as RR with
30 95% confidence interval (CI). WMD in days with 95% CI was calculated to express the excess
31 in LOS and ICU-LOS.

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3 1 Variation of the effect estimate was assessed by grouping the studies according to the following
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5 2 study/outcome characteristics: mortality time assessment (7 vs 14 days), aetiology (*E. coli* vs
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7 3 *K. pneumoniae*), clinical setting (paediatric, oncology, ICU), economic country areas (high-
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9 4 income countries [HICs] vs low- and medium-income countries [LMICs]), study design,
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11 5 assessment of empiric therapy, and year. The source of infection was assessed and analysis of
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13 6 mortality focused on BSIs while LOS was determined for BSIs and non-invasive infections
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15 7 (i.e., urinary tract infections, respiratory tract infections, surgical site infection) due to limited
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17 8 reporting.

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18 9 Subgroup analysis was computed only if more than 2 studies were available for each group.
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20 10 Heterogeneity was evaluated by using I^2 statistics and metaregression. Overall significance
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22 11 testing was carried out using Wald tests adjusted using the Bonferroni correction. The
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24 12 unadjusted ORs were compared with the adjusted ORs to estimate the effect of adjustment.
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26 13 Reporting and publication bias was presented in funnel plots (supplementary figure 1 and 2)
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28 14 and tested by Egger's test. Statistical analyses were performed using Stata version 15. Risk of
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30 15 bias was assessed independently by two authors (PS, DL) using the Newcastle - Ottawa
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32 16 quality assessment scale for cohort studies.⁶ Studies were classified as low, moderate, or
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34 17 high quality according to AHRQ standards (supplementary table S2). All meta-analyses
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36 18 were performed in accordance with the Cochrane Collaboration recommendations⁷ and
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38 19 reported according to the PRISMA statement.⁸

37 20 The protocol is available online.

39 21 ([https://im1-tuebingen.de/wp-](https://im1-tuebingen.de/wp-content/uploads/2019/03/ClinicalImpactAMR_SR_studyprotocol_2018.pdf)
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41 22 [content/uploads/2019/03/ClinicalImpactAMR_SR_studyprotocol_2018.pdf](https://im1-tuebingen.de/wp-content/uploads/2019/03/ClinicalImpactAMR_SR_studyprotocol_2018.pdf))

43 23 **Patient and Public Involvement**

45 24 There was no patient or public involvement in this systematic review of published literature.

47 25 **RESULTS**

50 26 Our literature search identified 1006 studies, and 92 (9.2%) met the eligibility criteria on the
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52 27 basis of abstract screening. Full-text screening excluded an additional 5 articles, providing an
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54 28 evidence base of 87 studies (Figure 1).⁹⁻⁹⁵ The 87 studies included in the qualitative analysis
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56 29 were conducted between 1991 and 2017 in 25 countries, mainly in South Korea (14 studies),
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58 30 Thailand (7), USA (7), Taiwan (7), and Spain (7). Sixty (68.9%) studies were performed in
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60 31 HICs, 26 (29.9%) in LMICs, and 1 included both HICs and LMICs.⁵⁵ About half (44, 50.6%)
32 32 were retrospective cohort studies, 24 (27.6%) case cohort studies, and 18 (20.7%) prospective

1 cohort studies; 1 study had an interventional design.⁵⁶ The comparison group was patients with
2 infections caused by gram-negative non-ESBL producers in 82 (94.3%) studies, non-infected
3 patients in 2 (2.3%), and both control groups in 3 (3.5%). Most (57, 65.5%) studies included
4 data from the entire hospital, while a few focused on specific settings, mainly ICUs (9, 10.3%)
5 and paediatric wards (8, 9.2%). The most common ESBL-producing bacteria were *E. coli* (23,
6 26.4%) and *K. pneumoniae* (17, 19.5%). An overview of study characteristics is provided in
7 online supplementary table S3.

8 Because data in 3 studies^{21,60,86} were insufficient for quantitative analysis, 84 (96.6%) studies
9 were included in the meta-analysis analysing data from 22,030 patients and 149 outcome
10 measures. Fifty-seven studies analysed BSIs and 10 non-invasive infections. Study
11 characteristics for all studies are provided in online supplementary table S4. 49 (58.3%) studies
12 were of high quality, 23 (27.3%) were of moderate quality, and 12 (14.3%) were of low quality
13 (supplementary table S5).

14 **All-cause mortality**

15 All-cause mortality was reported in 81 studies including 21,942 patients (56 on BSIs and 7 on
16 non-invasive infections). ESBL production in patients with BSIs increased all-cause mortality
17 by a factor of 1.70 (95% CI: 1.52-1.90; $p<0.001$; $I^2=45.3%$; $p<0.001$). The RR increased over
18 time from 1.56 (95% CI: 1.15-2.11; $p=0.004$) in 1991-1999 to 1.74 (95% CI: 1.50-2.01;
19 $p<0.001$) in 2000-2009, and it was stable in 2010-2018 (1.72, 95% CI: 1.39-2.13; $p<0.001$).
20 The RR was higher in studies assessing appropriateness of empiric therapy (RR=1.75; 95% CI
21 1.54-1.99; $p<0.001$) than in those that did not (RR=1.55; 95% CI 1.26-1.90; $p<0.001$). The
22 subgroup analysis by pathogen showed that ESBL production increased the RR in BSIs due to
23 *E. coli* (RR=1.82; 95% CI: 1.50-2.21; $p<0.001$) compared to those due to *K. pneumoniae*
24 (RR=1.48; 95% CI: 1.17-1.87; $p=0.001$). Stratification by population age showed a higher RR
25 in paediatric population (RR=2.09; 95% CI: 1.62-2.71; $p<0.001$). Effect estimates did not vary
26 significantly by study country, mortality time assessment (14 vs 28 days), ESBL molecular
27 resistance mechanisms, or study design (Figure 2 and online supplementary figure 3). Adjusted
28 estimates for inappropriate empirical antibiotic therapy were provided for 14 studies. The
29 pooled unadjusted OR for all-cause mortality was 2.91 (95% CI: 2.23-3.81; $p<0.001$, $I^2=27.1%$;
30 $p=0.164$) and the pooled OR after adjusting for receipt of appropriate empirical treatment was
31 3.22 (95% CI: 1.53-6.76; $p=0.002$; $I^2=87.5%$; $p<0.001$).

32 Studies with non-invasive infections reported a RR of 1.58 (95% CI: 1.23-2.02; $p<0.001$)
33 (supplementary figure 4).

1 **Attributable mortality**

2 Attributable mortality was analysed in 16 studies including 2,885 patients. All studies were
3 performed in HICs. ESBL production in patients with BSIs increased the risk of attributable
4 mortality by a factor of 1.75 (95% CI: 1.45-2.11; $p<0.001$; $I^2=0\%$; $p<0.001$). The RR increased
5 over time from 1.53 (95% CI: 1.10-2.12; $p=0.011$) in 1991-1999 to 1.91 (95% CI: 1.43-2.54;
6 $p<0.001$) in 2000-2009 (Figure 3). Pathogen-specific RR for attributable mortality was 1.60
7 (95% CI: 1.18-2.15; $p=0.002$) for *K. pneumoniae* and 1.76 (95% CI: 1.33-2.34; $p<0.001$) when
8 the gram-negative organisms were analysed all together without species differentiation. The
9 subgroup analysis showed the RR was lower in case cohort studies (1.56; 95% CI: 1.09-2.25;
10 $p=0.016$) than in cohort studies (1.80; 95% CI: 1.37-2.37; $p<0.001$).

11 **Length of stay**

12 LOS data were provided in 37 studies (17 on BSIs and 8 on non-invasive infections) analysing
13 38 outcome measures. The WMD of LOS in patients with BSIs was 4.41 days (95% CI: 3.37-
14 5.46; $p<0.001$) and decreased from 5.72 days (95% CI: 2.69-8.75; $p<0.001$) in 1991-1999 to
15 4.22 days (95% CI: 3.02-5.43; $p<0.001$) in 2000-2009 and was stable up to 2018 (4.30 days;
16 95% CI: 1.38-7.22; $p=0.004$). Higher WMD ($p<0.001$) was observed for BSIs due to *K.*
17 *pneumoniae* (7.67 days; 4.63-10.71) than for those due to *E. coli* (6.07 days; 95% CI 3.71-8.43).
18 Retrospective cohort studies reported higher ($p<0.001$) WMD (6.43 days; 95% CI: 4.66-8.21;
19 $p<0.001$) than case cohort studies (3.32 days; 95% CI: 2.03-4.61). Studies in HICs showed
20 higher WMD (4.56 days; 95% CI 3.43-5.70; $p<0.001$) than studies in LMICs (3.55 days; 95%
21 CI 0.84-6.26; $p=0.01$) (Figure 4).

22 Studies with non-invasive infections reported a WMD of 2.19 days (95% CI: 1.56-2.81;
23 $p<0.001$), which decreased from 7.66 (95% CI: 5.83-9.46; $p<0.001$) in 2000-2009 to 1.44 (95%
24 CI: 0.77-2.10; $p<0.001$) in 2010-2018 (online supplementary figure 5).

25 The data on ICU-LOS were provided in 7 studies and showed that BSIs caused by ESBL
26 producers had a WMD of LOS of 3.07 days (95% CI: 1.61-4.54; $p<0.001$).

27 Heterogeneity of the studied effect-modifiers did not reach statistical significance when
28 assessed by metaregression (supplementary table S6).

29 Sensitivity analysis based on the quality of studies revealed no notable difference in the effect
30 estimates after exclusion of low-quality studies (data not shown). Egger's test and the funnel
31 plots (online supplementary figure 1 and 2) showed evidence for small study effects ($p<0.001$)
32 and publication bias.

1 DISCUSSION

2 This systematic review shows that ESBL production has a significant impact on the most
3 relevant patient-related clinical outcomes. In the subgroup analyses, all-cause mortality,
4 attributable mortality, and LOS both in hospital and in ICU were higher for patients with BSIs
5 due to ESBL-producing *Enterobacteriaceae* than for patients with BSIs due to non-ESBL-
6 producing strains. Non-invasive infections caused by ESBL-producing strains were associated
7 with higher all-cause mortality and prolonged LOS. Within the limitation of the low number of
8 studies evaluating specific patient populations, paediatric and cancer patients seemed to suffer
9 a higher impact of ESBL invasive infections than the overall population. Stratifying by
10 pathogen type, the impact of ESBL production was higher for *E. coli* BSIs than for *K.*
11 *pneumoniae* BSIs. No relevant differences in mortality analysis emerged with stratification by
12 study design or country income level. Impact of ESBL infections on mortality became more
13 evident in more recent studies. Studies reporting on appropriateness of empirical therapy, ESBL
14 resistance mechanisms, and MICs showed a higher clinical impact of ESBL infections than
15 studies not assessing these variables. In particular, pooled ORs adjusted for inappropriate
16 empirical treatment, showed a remarkably higher OR for mortality in patients with ESBL
17 infections.

18 Our findings confirm the results of previous systematic reviews. Schwaber et al. performed a
19 systematic review comparing mortality in ESBL BSIs and non-ESBL BSIs in studies published
20 through 2003.² The authors show a pooled RR for all-cause mortality of 1.85 but, in contrast to
21 our study, they combined *E. coli*, *Klebsiella* spp., and *Proteus* spp. in the analysis because of
22 sample size limitations. Rottier et al. analysed studies published through 2010 and adjusting
23 results for inappropriate empirical treatment found an adjusted OR of 1.37.³ Our study, adding
24 more than 50 studies in 17 years to the Rottier systematic review, confirmed the clinical
25 importance of ESBL production to all-cause mortality and for the first time assessed the role of
26 ESBL production on attributable mortality. We addressed relevant effect-modifiers through
27 subgroup analyses and found that population, pathogen, and assessment of empiric therapy all
28 had an impact on estimates. Because we believe that appropriate empirical treatment plays a
29 relevant role in invasive infections, we performed a secondary analysis by pooling only adjusted
30 ORs and confirming the significant impact of antibiotic resistance as already shown in a
31 previously published systematic review.⁹⁶ The lack of consideration of appropriateness of
32 therapy in the studies evaluating mortality seems to underestimate the risk of ESBL production
33 on mortality. However, studies assessing the impact of appropriate therapy did not provide

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3 1 homogeneous definition and could refer either to empirical or definite therapy or a single
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5 2 component irrespective of the dosage, making results difficult to interpret. The impact of ESBL
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7 3 production on LOS has been also estimated, assessing BSIs and non-invasive infections
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9 4 separately and confirming the prolongation of hospitalisation.

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11 5 Our systematic review contributes to the discussion on the limitation of current evidence for
12
13 6 the estimation of mortality due to antibiotic-resistant infections. Our finding underlines the
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15 7 importance of considering a multivariable model with a whole set of determinants when trying
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17 8 to quantify the impact of resistance on clinical outcomes. The source of infection, for example,
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19 9 can influence the role of empirical treatment on the clinical outcome. For example, patients
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21 10 with UTI receiving inappropriate empirical antibiotic therapy can potentially show a favourable
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23 11 outcome, most probably due to the high concentration of antibiotic reached in the urinary
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25 12 tract.⁹⁷

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27 13 Our study has some limitations. Although results of the meta-analyses were significant in all
28
29 14 the subgroups, we could analyse only a limited number of studies providing information for
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31 15 subgroups such as haematological patients and low-income countries, making generalizability
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33 16 of results less certain for these specific patient populations. Only a few studies reported MIC
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35 17 data or specific ESBL molecular resistant phenotype (i.e., AmpC). Moreover, publication bias
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37 18 was detected in both the main analyses (all-cause mortality and LOS), thus implying the
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39 19 possibility that results from small studies with non-significant results might have been
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41 20 conducted and not published, resulting in a possible overestimation of our results. The non-
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43 21 homogeneous reporting of some relevant data in published literature (e.g., disease severity,
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45 22 underlying comorbidities and resistance mechanism) may also have affected the precision of
46
47 23 the estimate. Patients with ESBL are intrinsically at higher risk of mortality and complications
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49 24 because they are often older, have more comorbidities or higher antibiotic exposure, and are at
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51 25 higher risk of receiving inappropriate empirical treatment.⁹⁸ Finally, due to resource constraints,
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53 26 we had to limit our search to PubMed database with the chance of missing relevant studies.

54
55 27 In summary, our systematic review emphasises the importance of suspicion and confirmation
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57 28 of ESBL production as soon as possible for invasive infections and demonstrates that ESBL
58
59 29 production increases the risk of attributable mortality and LOS in both hospital and ICU for
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30 invasive and non-invasive infections. Patients with ESBL infections remain at higher risk of
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32 mortality and prolonged LOS even after adjustment for empiric inappropriate treatment.
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34 Control for other relevant effect-modifiers is hindered by the sparseness of published data.
35
36 Future studies addressing the clinical burden of drug-resistant infections must include ESBL

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3 1 production and should assess both the impact of molecular mechanisms of resistance and effect
4 2 on specific patient populations such as haematological patients and those in LMIC.

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6
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9
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14 8 reviewed the paper. All authors read, edited, and approved the final manuscript. The
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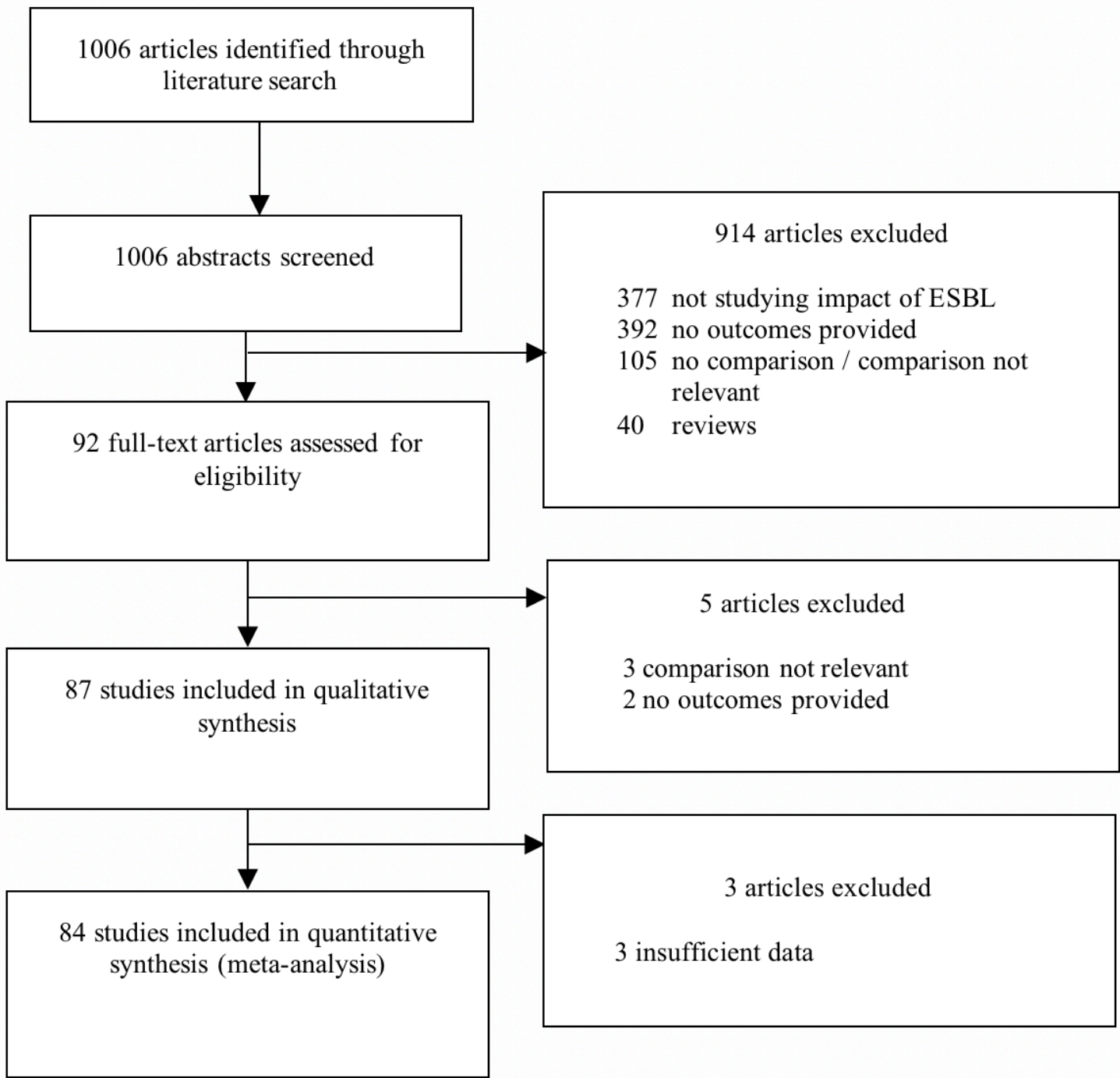
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3 **1 FIGURE LEGENDS**

4 2
5 3 Figure 1: Literature search and study inclusion and exclusion

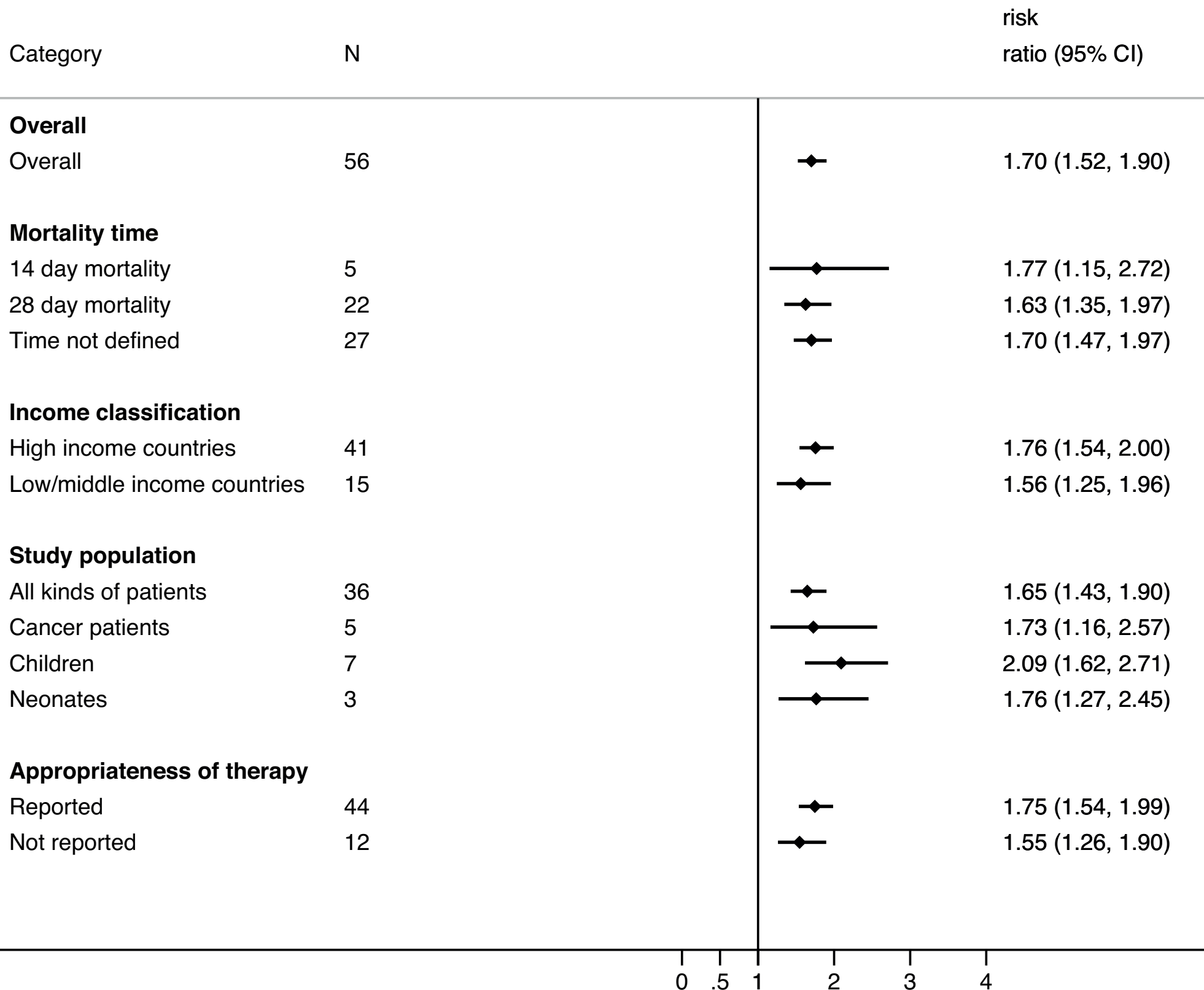
6 4
7 5 Figure 2: Pooled risk ratios for all-cause mortality in patients with ESBL bloodstream
8 6 infections compared to patients with non-ESBL bloodstream infections— subgroups not
9 7 included in attributable mortality

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11 9 Figure 3: Pooled risk ratios for attributable mortality in patients with ESBL bloodstream
12 10 infections compared to patients with non-ESBL bloodstream infections

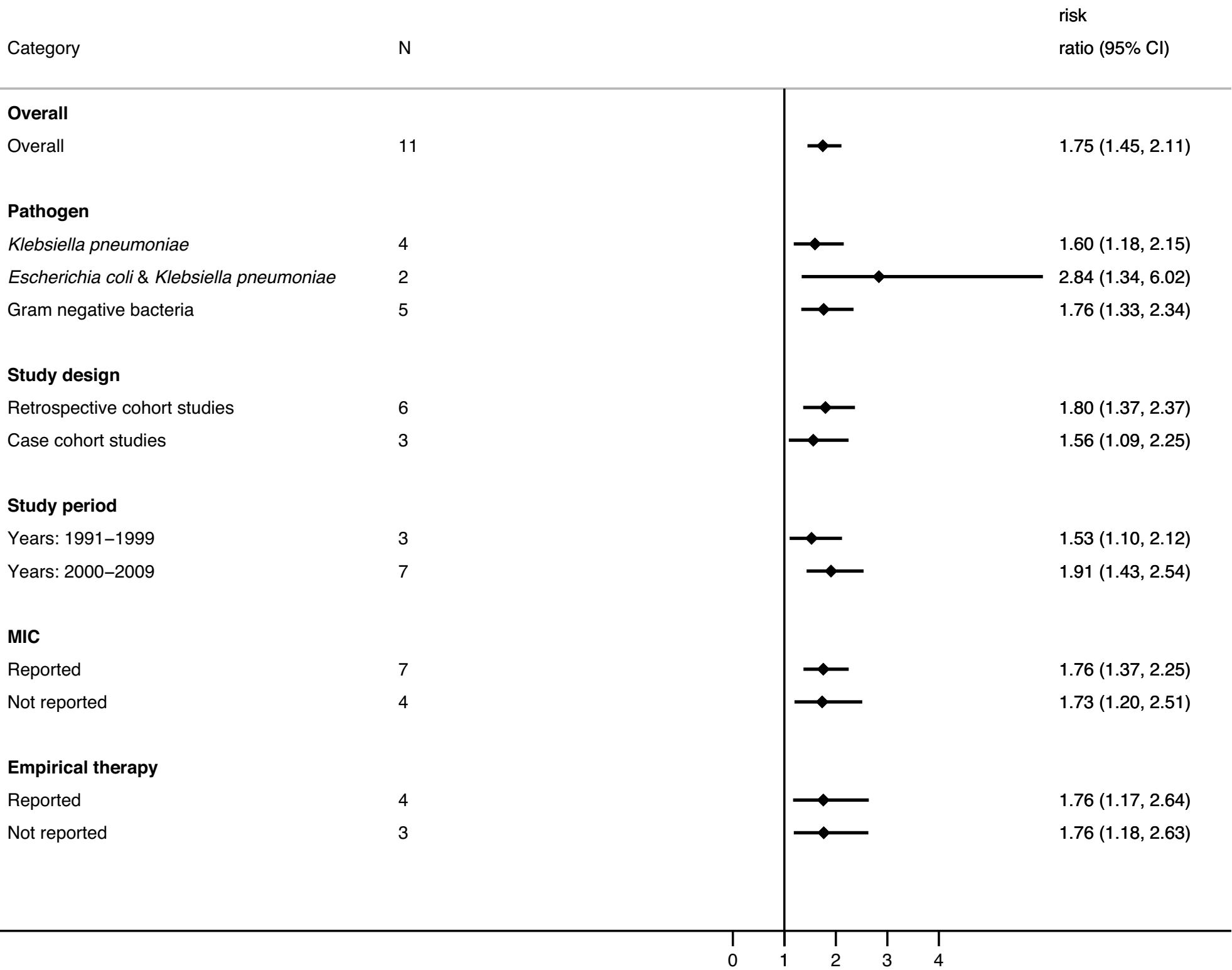
13 11
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15 13 infections compared to patients with non-ESBL bloodstream infections
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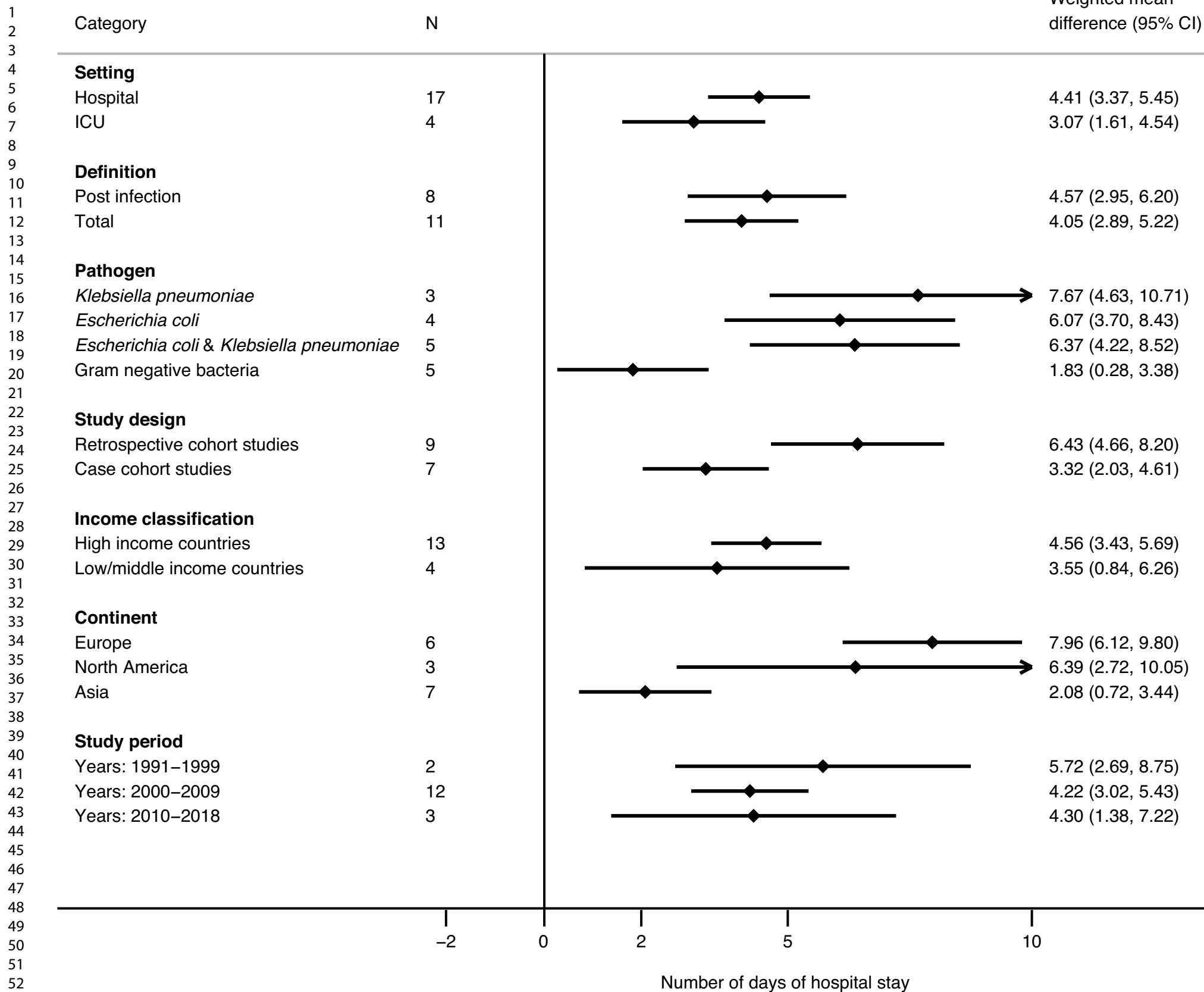


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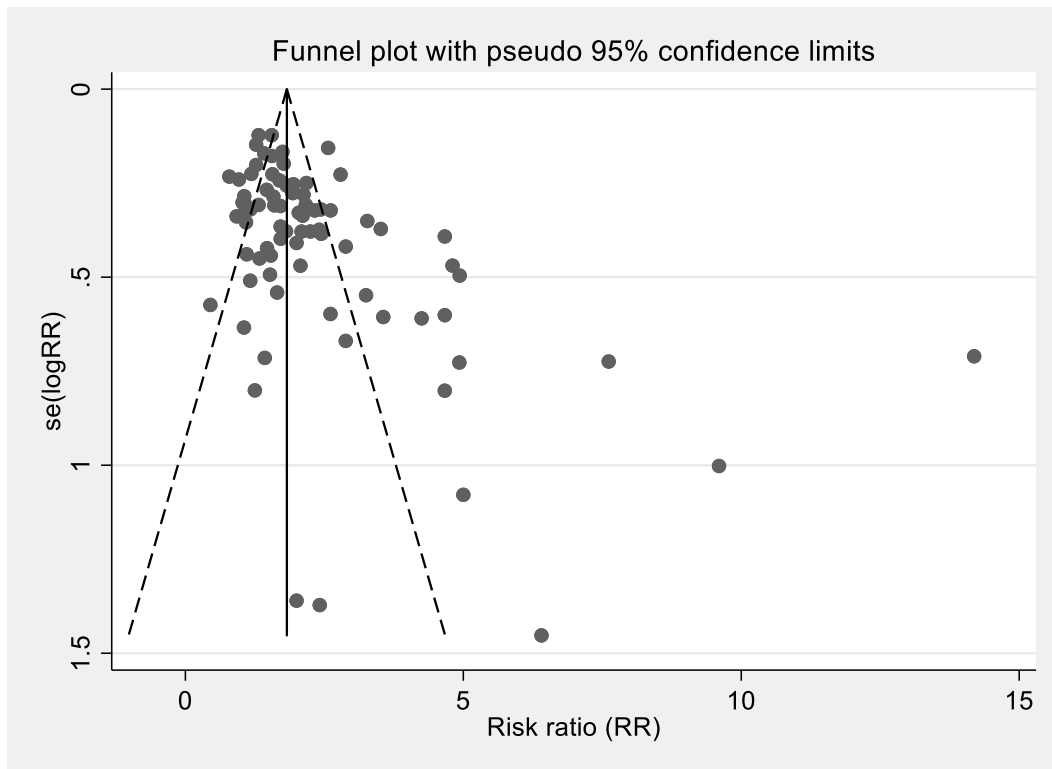


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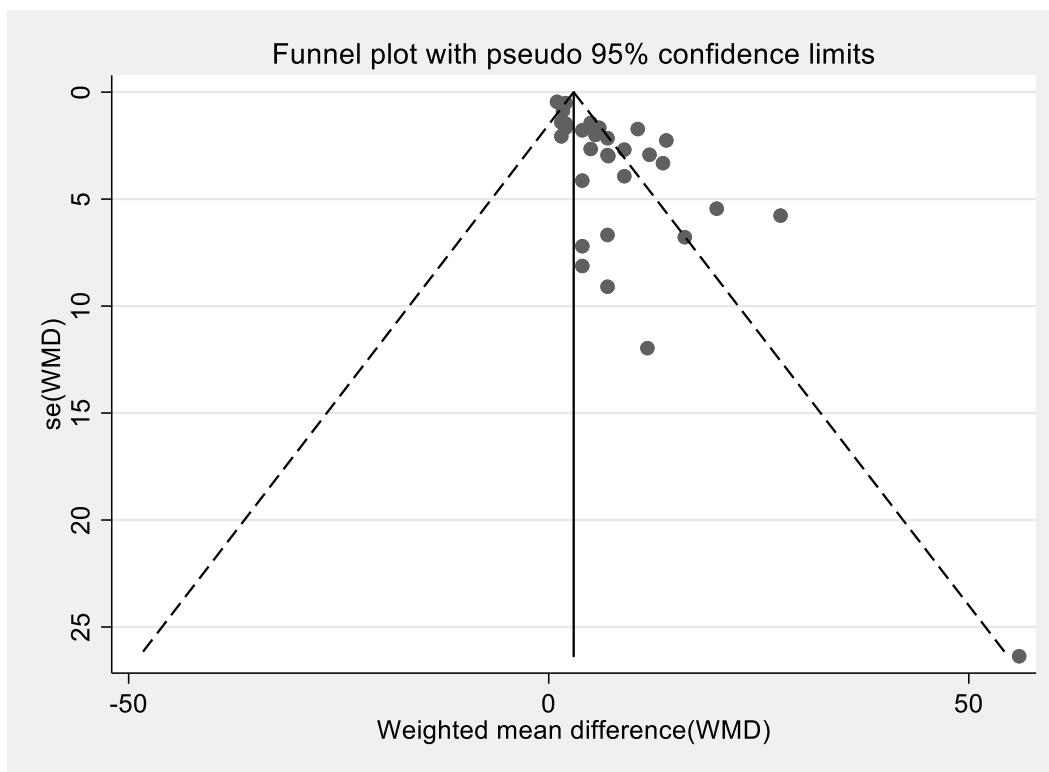


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3 **Supplementary figure 1: Funnel plot of risk ratios for all-cause mortality in patients with ESBL bloodstream**
4 **infections compared to patients with non-ESBL bloodstream**
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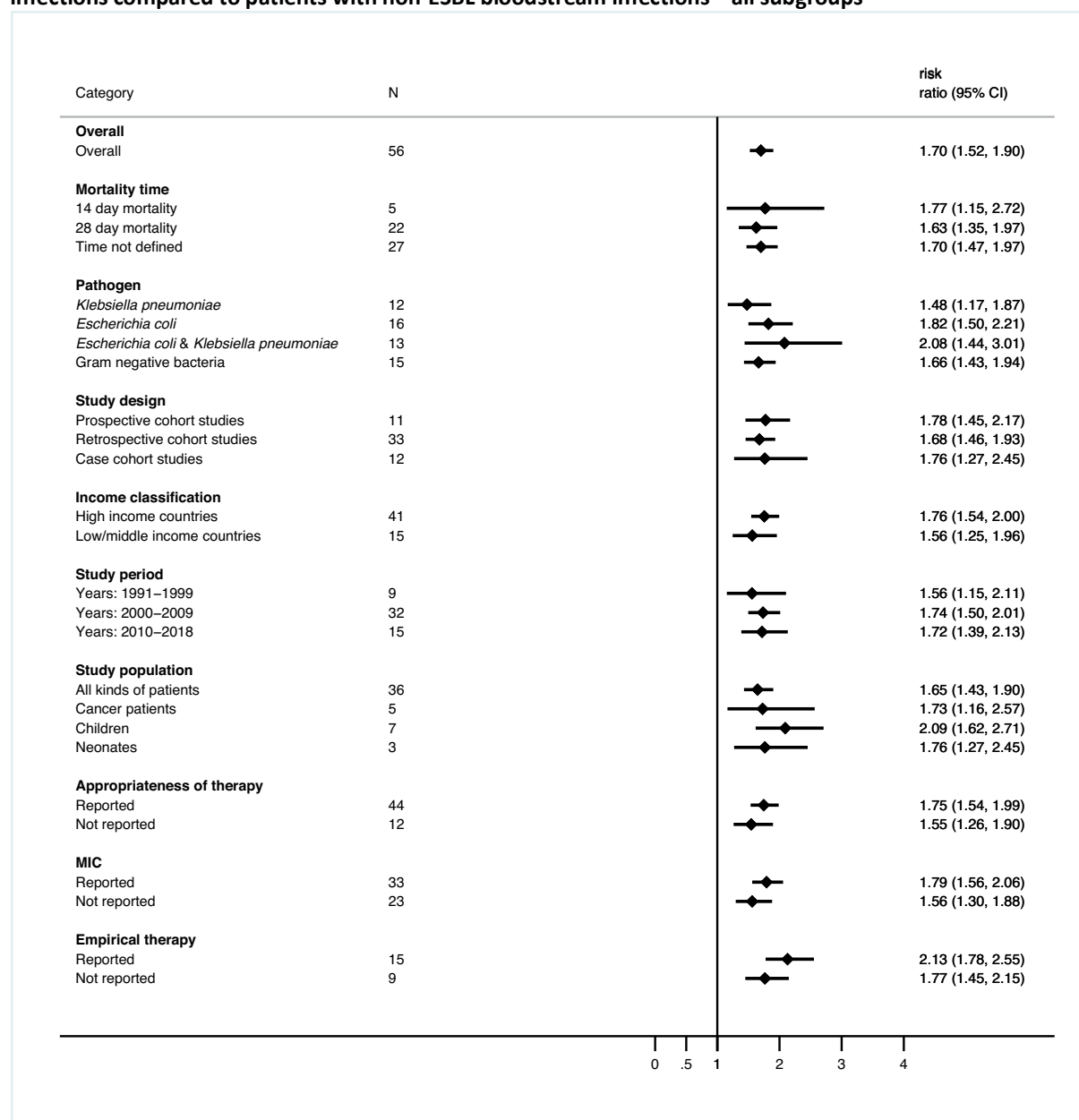
The y axis $se(\log RR)$ is the standard error of the log risk ratio. Pseudo 95% confidence limit refers to the 95% confidence limits around the summary treatment effect for each standard error on the vertical axis and to the expected distribution of studies in the absence of heterogeneity or of selection biases.

Supplementary figure 2: Funnel plot of weighted mean differences in the length of stay for patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections

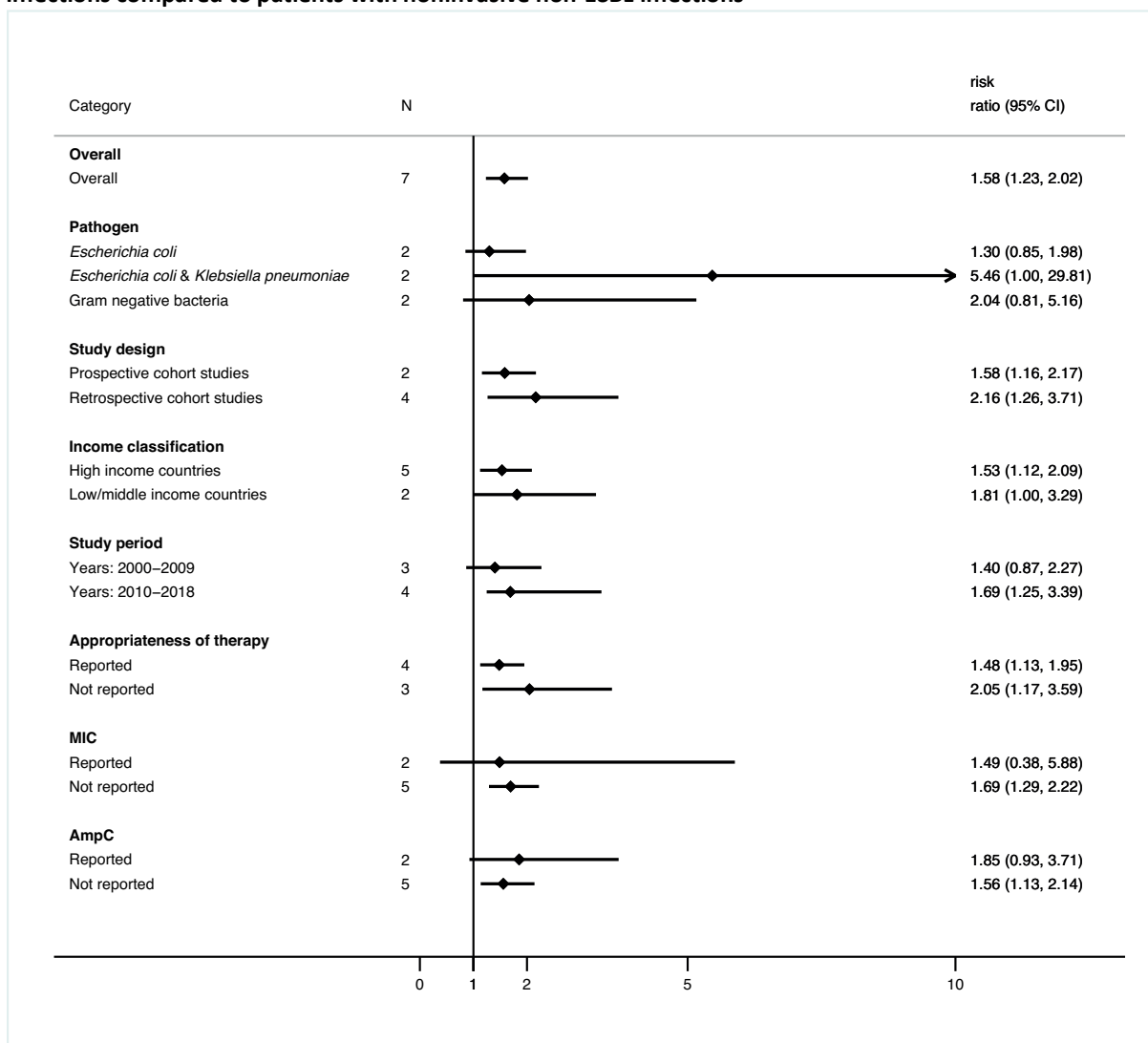


The y axis $se(WMD)$ is the standard error of the weighted mean difference. Pseudo 95% confidence limit refers to the 95% confidence limits around the summary treatment effect for each standard error on the vertical axis and to the expected distribution of studies in the absence of heterogeneity or of selection biases.

Supplementary figure 3: Pooled risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections—all subgroups

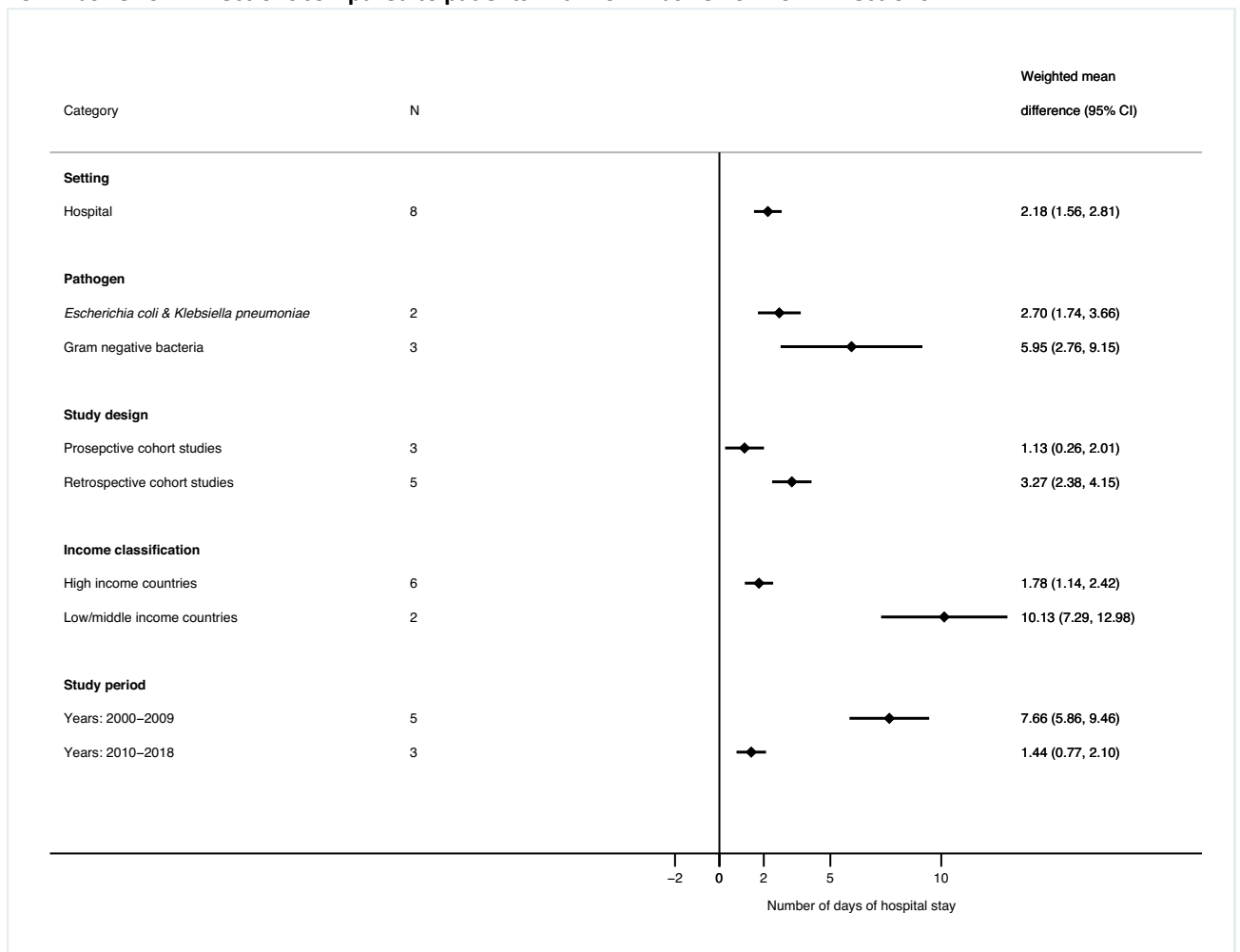


Supplementary figure 4: Pooled risk ratios for all-cause mortality in patients with noninvasive ESBL infections compared to patients with noninvasive non-ESBL infections



Only

Supplementary figure 5: Weighted mean differences in length of hospital stay in patients with noninvasive ESBL infections compared to patients with noninvasive non-ESBL infections



Supplementary table S1: Search terms used in PubMed :

((ESBL[tw] OR ""Extended spectrum beta-lactamase""[tw] OR ESBL[Mesh] OR ""Extended spectrum beta-lactamase"" [Mesh]) OR Extended spectrum ? lactamase[tw] OR Extended spectrum ? lactamase[Mesh])

AND

(Escherichia Coli[Mesh] OR E.coli[Mesh] OR Escherichia Coli[tw] OR E.coli[tw])) OR (Klebsiella pneumoniae[Mesh] OR K.Pneumoniae[Mesh] OR Klebsiella pneumoniae[tw] OR K.Pneumoniae[tw])

Coupled with

(length of stay[mesh] OR (hospitalisation[tw] AND length[tw]) OR length of hospitalisation[tw] OR length of hospitalization[tw] OR duration of hospitalization[tw] duration of hospitalisation[tw] OR LOS[tw] OR ((period[tw] OR length[tw]) AND (hospital stay[tw] OR hospitalisation[tw] OR hospitalization[tw])) OR

(mortality[mesh] OR mortality[tw] OR death rate[tw] OR fatality[tw] OR survival rate[tw] OR death[tw] OR died[tw] OR dead[tw])) OR

(cost*[Title/Abstract] OR "costs and cost analysis"[MeSH:noexp])

Coupled with

("0001/01/01"[PDat] : "2018/10/01"[PDat]))

Supplementary table S2: Modified Newcastle Ottawa quality assessment scale for case-control studies and cohort studies.

For case cohort studies, the quality criteria assessed are			
1	Is the case definition adequate?	a*	yes, with independent validation
		b	yes, eg. record linkage or based on self-report
		c	no description
2	Representativeness of the cases	a*	consecutive or obviously representative series of cases
		b	potential for selection biases or not stated
3	Selection of Controls	a*	community controls
		b	hospital controls
		c	no description
4	Definition of Controls	a*	no history of disease (endpoint)
		b	no description of source
5	Comparability of cases and controls on the basis of the design or analysis	a*	study controls for at least one variable (including age, sex and comorbidities)
		b**	study controls for more than one variable (including age, sex and comorbidities)
6	Ascertainment of exposure	a*	secure record (eg surgical records)
		b	structured interview blind to case/control status
		c	interview not blinded to case/control status
		d	written self-report or medical record only
		e	no description
7	Same method of ascertainment for cases and controls	a*	yes
		b	no
		c	unclear
8	Non-Response rate	a	same rate for both groups
		b	non respondents described
		c	rate different and no designation
For cohort studies, the quality criteria assessed are			
1	Representativeness of the exposed cohort	a*	truly representative
		b*	somewhat representative
		c	selected group of users
		d	no description
2	Selection of the non-exposed cohort	a*	drawn from the same community as the exposed cohort
		b	drawn from a different source
		c	no description of the derivation of the non-exposed cohort
3	Ascertainment of exposure	a*	secure record (eg surgical records)
		a*	structured interview
		c	written self-report
		d	no description
4	Demonstration that outcome of interest was not present at start of study	a*	yes
		b	no
		c	unclear
5	Comparability of cohorts on the basis of the design or analysis	a*	study controls for age or comorbidities
		b**	study controls for age and comorbidities
6	Assessment of outcome:	a*	independent blind assessment
		b*	record linkage
		c	self-report
		d	no description

7	Follow-up long enough for outcomes to occur	a*	yes
		b	no
		c	unclear
8	Adequacy of follow up of cohorts	a*	complete follow up – all that matters subjects accounted for, subjects lost to follow up unlikely to introduce bias - small number
		b*	inadequate numbers but description provided of those lost
		c	inadequate follow up rate and no description of those lost
		d	no statement

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

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Supplementary table S3: Study characteristics overview

Subgroup	All Studies	Bloodstream infections	Noninvasive infections
	87	57	10
Country			
South Korea ^{11,12,14,15,29,33,36,40,42,44,49,50,55,57}	14	9	2
Thailand ^{22,24,43,51-53,86}	7	3	
USA ^{8,16,26,30,46,59,67}	7	2	1
Spain ^{34,38,56,60,68,89,92}	7	4	2
Taiwan ^{10,37,62,69,80,82,94}	7	5	2
China ^{58,71,72,75,85}	5	4	
Israel ^{21,45,90,91}	4	3	
Germany ^{9,39,41,61}	4	3	
Italy ^{23,31,35}	3	3	
Japan ^{74,79,84}	3	3	
Tanzania ^{17,64,73}	3	3	
India ^{47,48,78}	3	1	1
Canada ^{63,65,83}	3	2	
UK ^{20,28,87}	3	3	
France ^{66,77}	2	1	1
South Africa ^{13,81}	2	1	
Brazil ^{13,81}	2	2	
Greece ⁸⁸	1	1	
Hungary ⁹³	1	1	
Lebanon ²⁵	1	-	
Malaysia ²⁷	1	-	1
Mexico ⁷⁰	1	1	
Saudi Arabia ¹⁸	1	1	
Turkey ⁷⁶	1	1	
Continent			
Asia ^{10-12,14,15,18,21,22,23,25,27,29,33,36,37,40,42-45,47-53,55,57,58,62,69,71,72,74,74,78-80,82,84-86,90,91,94}	46	29	6
Europe ^{9,20,23,28,31,34,35,38,39,41,56,60,61,66,68,76,77,87-89,92,93}	22	17	3
North America ^{8,16,26,30,46,59,63,65,67,83}	10	4	1
Africa ^{13,17,64,73,81}	5	4	-
South America ^{19,32,70}	3	3	-
More than 1 continent ⁵⁴	1	-	-

Income group			
High-income countries ^{8-12,14-16,18,20,21,23,26,28-31,34-42,44-46,49,50,55-57,59-63,65-69,74,77,79,80,82-84,87-94,}	60	41	8
Low- and middle-income countries ^{13,17,19,22,24,25,27,32,43,48,51-53,58,64,70-73,75,76,78,81,85,86}	26	16	2
High-income countries AND Low- and middle-income countries ⁵⁴	1	-	-
Study design			
Case cohort study ^{8,10,22-26,29,38,42,44,53,56,59,61-63,65-67,83-85}	24	14	
Retrospective cohort study ^{9,11-15,18,19,21,27,31-36,39-41,43,45,46,48-52,57,58,69,71,72,74-76,79-82,86,87,91,93,94}	44	32	
Prospective cohort study ^{16,17,28,30,37,47,54,60,64,68,70,73,77,78,88-90,92}	18	11	
Year group			
1991-1999 ^{8,58,13,14,15,60,19,23,26,34,44,91,92}	13	10	-
2000-2009 ^{9-12,16-18,20-22,24,25,27-33,35-43,45,47-50,52,53,55,56,59,61,62,65-67,87-90,93,94}	49	31	6
2010-2018 ^{46,51,52,57,63,64,68-86}	25	16	4
Pathogen			
<i>Escherichia coli</i> ^{9,22,28,31,33-35,38,41,43,50,53,56,57,66,68,69,71,74,84,85,89,92}	23	16	3
<i>Klebsiella pneumoniae</i> ^{13,14,18,19,23,27,30,32,39,41,45,59,60,72,76,81,93,94}	17	11	1
<i>E. coli</i> and <i>K. pneumoniae</i> ^{8,11,12,15,24,26,36,41,42,44,46,48,49,52,55,58,61,67,83,86,87}	20	13	2
Gram-negative bacteria ^{10,16,17,20,21,25,29,37,40,47,51,54,62-65,70,73,75,77-80,82,88,90,91}	27	17	4
Study setting			
Entire hospital ^{8,9,14,16,18-25,27,28,31-36,38-44,46-48,50-53,56-58,60,63-67,71,72,74,80,83,84,88-94}	57	40	7
Intensive care unit ^{30,59,62,73,77-79,86,87}	9	5	1
Pediatric ward ^{15,17,26,49,55,76,81,86}	8	7	-
Neonatal ward ^{13,59,62,69,73}	5	3	-
Neonatal intensive care unit ^{59,62,73}	3	2	-
Medical ward ^{11,37,68}	3	-	2
Not provided ^{29,45}	2	-	-
Emergency Department ^{10,82}	2	2	-
Surgical ward ^{30,54}	2	-	-
Burn unit ³⁰	1	-	-
Oncology ⁷⁰	1	1	-
Referral centre for hepatopacreaticobiliary diseases ⁷⁵	1	-	-
Hematological ¹²	1	1	-

Study population			
All kinds of patients ^{8-11,12,16,18-25,27,28,32,33,37-39,41-44,46-48,50-54,56,58,60,61,63-67,74,80,82-84,88,90-93}	55	36	7
Intensive care unit patients ^{30,77-79,85,87}	6	3	1
Children ^{15,17,26,49,55,76,81,86}	8	7	-
Neonates ^{13,59,62,69,73}	5	3	-
Cancer patients ^{31,49,57,70,89}	5	5	-
Immunocompromised patients ⁴⁹	1	1	-
Diabetic patients ⁹⁴	1	1	-
Elderly patients ⁶⁸	1	-	1
Patients with chemotherapy/stem cell transplantation ^{12,89}	2	2	-
Patients after prostatitis biopsy ⁴⁰	1	-	1
Lungs transplantation patients ⁴⁵	1	-	-
Hematological patients ⁷¹	1	1	-
All except cardiothoracic therapy, transplant surgery, burns ⁷²	1	1	
Patients with pyogenic liver abscess ⁷⁵	1	-	-
Data reported			
Treatment information ^{8,10-11,21-24,28-36,38,42-47,49,50,52-63,65,66,68-94}	74	50	6
Appropriateness of treatment ^{8,10-12,14,15,17-19,21-24,28-36,38,42-44,46,47,49,50,52-54,56-58,60-63,65,66,68,70-72,74,75,77,79,81-84,87-94}	62	45	5
Empirical therapy ^{12,14,15,22,23,31,33-36,38,42,49,50,54,56,57,61,74,79,81,92}	22	16	2
Treatment outcome ^{8,10-19,23,24,28-36,38,42-47,49,50,52-55,57-63,65,66,70-72,74,76-79,81-84,86-90,92-94}	64	45	3
Minimum inhibitory concentration results ^{8,9,11,12,14-17,20-23,25,26,30,31,33-39,41,42,45,48-50,52-57,60,61,64,66,67,74-76,78,79,81,83-85,87,92,93}	52	34	4
AmpC genotyping ^{8,9,15,30,39,44,48,54,55,63,64,68,84}	13	6	2

Supplementary table S4: Characteristics for each study

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Lautenbach E ⁸	1997-1998	USA	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality; LOS	Risk factors for infection with ESBL-producing pathogens, difference in clinical outcomes of infections: resistant vs. susceptible organisms	EC, KP
Kim SH ¹²	2007-2008	South Korea	Cohort study, Retrospective	Non-ESBL-infection	Patients who received either chemotherapy or stem cell transplantation; neutropenic fever	Hematological ward, Others	All-cause mortality (28 day)	Risk factors for acquisition of ESBL, appropriateness of empirical antimicrobial therapy, clinical outcomes in relation to ESBL production	EC, KP
Chayakulkeere M ⁵¹	2015-2015	Thailand	Cohort study, Retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Prevalence & risk factors for infections with & antibiotic susceptibility patterns of & outcomes of patients infected with ESBL-producing-GNB	GNB
Pisarntharak A ⁵²	2003-2007	Thailand	Cohort study, Retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Predictors for mortality associated with community-onset BSI with ESBL-producing pathogens, initial empirical antimicrobial regimens, associated hospital resource utilisation, costs accrued after diagnosis of BSI	EC, KP
Pisarntharak A ⁵³	2003-2004	Thailand	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Mortality associated with community-onset infection due to ESBL-producing pathogens, associated hospital resource use, post-infection hospital cost	EC
Jean SS ⁵⁴	2010-2011	Portugal, Columbia, the Philippines, Taiwan, Thailand	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Surgical ward	Attributable mortality, LOS	Clinical impact on hospitalised patients with community-acquired complicated intra-abdominal infection: ESBL-producing- vs. non-ESBL-producing pathogens	GNB
Lee J ⁵⁵	1999-2005	South Korea	interventional studies	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality (28 day)	impact of a change in antibiotic policy on ESBL-prevalence	EC, KP
Briongos-Figuero A ⁵⁶	2009-2010	Spain	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Characteristics & associated risk factors for EBSL-enterobacteria-UTIs	EC
Ha YE ⁵⁷	2010-2012	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients with cancer	Entire hospital	All-cause mortality (28 day)	Clinical & molecular epidemiology of ESBL-EC bacteraemia, clinical impact of ESBLs on patient outcome	EC
Du B ⁵⁸	1997-1999	China	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors for nosocomial ESBL-EC- and ESBL-KP- bacteraemia & influence on patient outcome.	EC, KP

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen	
5	Stone PW ⁵⁹	2001	USA	Case cohort study	Non-ESBL-infection	Neonates at NICU	NICU	LOS	costs of interventions aimed at controlling the outbreak, attributable length of stay associated with infection and colonisation with ESBL-KP	KP
8	Pillay T ¹³	1995-1996	South Africa	Cohort study, retrospective	Non-ESBL-infection	Neonates	Neonatal ward	All-cause mortality	Use of piperacillin/tazobactam in treatment of KP- infection	KP
10	Kim BN ¹⁴	1999-2000	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, LOS	Prevalence & clinical characteristics of ESBL-KP- bacteraemia, impact of ESBL- production on outcome of patients with KP- bacteraemia in endemic situation.	KP
13	Kim YK ¹⁵	1993-1998	South Korea	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality	Risk factors & clinical outcomes & clinical responses to treatment of ESBL-EC- and ESBL-KP-bacteraemia, prevalence and types of their ESBLs	EC, KP
16	Bhavnani SM ¹⁶	2001-2002	USA	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Risk factors for occurrence of invasive ESBL-EC- and ESBL-KP-infections, factors associated with clinical outcome, drug regimens for treatment of infections associated ESBL/non-ESBL strains in real-life clinical practice, clinical response rates for patients treated with cephalosporins/other classes of antimicrobial agents, /carbapenems, clinical response for those patients with infection associated with ESBL and non-ESBL-producing strains with MIC values V8 Ag/mL treated with cephalosporins.	GNB
24	Blomberg B ¹⁷	2001-2002	Tanzania	Cohort study, prospective	Non-ESBL-infection	Neonates, children	Pediatric ward	All-cause mortality	Prevalence & clinical implications of ESBL production in EC-,KP-, Salmonellae- septicemia	GNB
26	Pena C ⁶⁰	1993-1995	Spain	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Clinical epidemiology& outcome of ESBL-KP- bacteraemia, relevance of ESBL strains in mortality of patients with hospital-acquired KP-BSI.	KP
29	Kola A ⁶¹	2002-2004	Germany	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS, ICU-LOS	Outcomes of ESBL-EC- and ESBL-KP-infections	EC, KP
32	Isai MH ⁶²	2001-2012	Taiwan	Case cohort study	Control group: non-ESBL-infection, second control group: all hospitalised patients	Neonates at NICU	NICU	Attributable mortality, all-cause mortality, LOS	Clinical features& risk factors& molecular epidemiology of ESBL-GNB	GNB
36	Maslikowska JA ⁶³	2010-2013	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS	Differences in clinical & microbiological outcome, mortality, and/or hospital resource use: ESBL-EC- and ESBL-Ks- vs non-ESBL-EC- and non-ESBL-Ks-infections	GNB

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Onken A ⁶⁴	2012-2013	Tanzania	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Most common bacterial pathogens causing BSI, antimicrobial susceptibility	GNB
Nguyen ML ⁶⁵	2005-2010	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS, ICU-LOS	Risk factors for & patient outcomes associated with ESBL-EC- and ESBL-Ks- bacteraemia, appropriateness of empiric antibiotic therapy & effect of inappropriate empiric therapy on outcomes	GNB
Denis B ⁶⁶	2005-2009	France	Case-control study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day), LOS	Prevalence & risk factors for ESBL-EC bacteraemia, impact on length of stay & 30day mortality	EC
Chopra T ⁶⁷	2004-2009	USA	Case cohort study	Case 2(Control1): non-ESBL-infection, second control group: no infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Predictors of ESBL-EC- and ESBL-KP-BSI, focus on cefepime exposure.	EC, KP
Panhotra BR ¹⁸	2001-2003	Kingdom of Saudi Arabia	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors & clinical outcome of ESBL-KP-bacteraemia (hospital acquired)	KP
Marra AR ¹⁹	1996-2001	Brazil	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	ESBL-KP- associated mortality	KP
Skippen I ²⁰	2003-2005	UK	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors for & outcomes of ESBL-EC- and ESBL-KP-invasive transmission of organism in the healthcare setting	GNB
Schwaber MJ ²¹	2000-2003	Israel	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Outcomes of ESBL-production in Enterobacteriaceae-bacteraemia.	GNB
Apisarntharak A ²²	2003-2004	Thailand	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	All adult patients	Entire hospital	All-cause mortality, LOS	Clinical & molecular epidemiologic factors associated with community onset ESBL-EC- infections, hospital resource utilisation, estimate costs associated with medical care (hospitalised patients)	EC
Umbarello M ²³	1999-2003	Italy	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS, ICU-LOS	Factors associated with isolation of ESBL- KP-strains	KP
Zeistner R ⁹	2008-2010	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital,	All-cause mortality, LOS	Difference in mortality: ESBL-EC-BSIs vs. non-ESBL-EC-BSIs, molecular epidemiology of ESBL-positive isolates	EC

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	2003-2004	Thailand	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Risk factors for & outcomes of ESBL-EC- and ESBL-KP-infections (healthcare associated)	EC, KP
	2003	Lebanon	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Epidemiology of infections with ESBL-EC and ESBL-Ks at AUBMC risk factors & outcomes of infections - focus on effect of prior antibiotic administration & the risks imparted by specific classes of antimicrobial agents	GNB
	1999-2003	USA	Case cohort study	Non-ESBL-infection	Children	Entire hospital	All-cause mortality, LOS	Risk factors & outcomes associated with ESBL-EC-and ESBL-KP-BSI	EC, KP
	2003-2004	Malaysia	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Impact of ESBL-KP-respiratory tract infections on hospital mortality, requirement for mechanical ventilation & length stay	KP
	2003-2005	UK	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Differences in mortality & length of hospital stay & time from bacteraemia to death in patients with ESBL-EC- vs. non-ESBL-EC-bacteremic-infection	EC
	2000-2006	South Korea	Case cohort study	Non-ESBL-infection	Patients with spontaneous bacterial peritonitis	Not provided	All-cause mortality (28 day)	Outcomes of ESBL-EC-and ESBL-Ks- vs non-ESBL-EC-and ESBL-Ks-SBP (based on isolation from ascites), impact of ineffective initial antimicrobial therapy on outcome in patients with ESBL-EC- and ESBL-Ks-SBP, risk factors for infection by ESBL-producing microorganisms.	GNB
	2004-2008	USA	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU, Surgical ward, Burn unit	All-cause mortality (28 day)	ESBL types and strain variability, presence of host factors to determine potential role in morbidity and mortality during ESBL-KP-infections	KP
	2000-2007	Italy	Cohort study, retrospective	Non-ESBL-infection	Patients with hematological malignancies	Entire hospital	All-cause mortality (28 day)	Risk factors for mortality in patients suffering from hematological malignancies with concurrent EC-bacteraemia. Focus on impact of ESBL- production & fluoroquinolone resistance by bacterial isolates	EC
	2006-2009	Brazil	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day), LOS	Risk factors & mortality rate in ESBL-KP-bacteraemia	KP
	2008-2009	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Risk factors of ESBL-EC among community-onset bacteraemia, treatment outcomes	EC

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Pena C ³⁴	1996-2003	Spain	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Risk factors for mortality among patients with EC- infections	EC
Tumbarello M ³⁵	2006	Italy	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	ICU, Medical ward, Entire hospital, surgical wide	All-cause mortality (21 day), LOS	Clinical & economic impacts of ESBL production, inadequate Initial Antibiotic Therapy of EC-BSI	EC
Kang C ³⁶	2006-2009	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality (28 day)	Impact of ESBL-producing bacteraemia on outcome in patients with hematologic malignancy.	EC, KP
Wu YH ³⁷	2009-2012	Taiwan	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Medical ward	LOS	Host-related risk factors for community-onset UTI due to levofloxacin- or cefazolin-nonsusceptible isolates or uropathogens with ESBL production, clinical impact of UTIs due to antimicrobial-nonsusceptible pathogens	GNB
Rodriguez-Bano J ³⁸	2004-2006	Spain	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Epidemiology & risk factors (focus on previous antimicrobial use) & mortality rate for patients with ESBL-EC-COBSI	EC
Gürttnke S ³⁹	2008-2011	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Distribution of ESBL genotypes, hospital mortality in cases of ESBL-KP-BSI	KP
Oh MM ⁴⁰	2006-2011	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients after Prostatitis Biopsy	Entire hospital	LOS	Impact of ESBL-positive-strains on clinical course & progression to chronic prostatitis in patients with postbiopsy acute prostatitis.	GNB
Leistner R ⁴¹	2008-2011	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Financial disease burden attributable to ESBL-positive species in cases of EC-and KP-BSI	EC, KP
Lin JN ⁴⁰	2005-2009	Taiwan	Case cohort study	Non-ESBL-infection	All kinds of patients	Emergency Room	Attributable mortality, all-cause mortality (28 day), LOS, ICU-LOS	Clinical & microbiological characteristics, risk factors for acquisition of infection, prescription of initial empirical antibiotics mortality rate of infection	GNB
Yu NS ⁴²	2006-2010	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Clinical usefulness of breakpoints for treatment of Enterobacteriaceae-bacteraemia, (focus on EC- and Ks-bacteraemia): CLSI 2009- vs. CLSI 2010-guidelines.	EC, KP

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Anunnatsiri S ⁴³	2005-2006	Thailand	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Incidence of ESBL-EC-septicemia, factors associated with infection & clinical outcomes	EC
Kang CI ⁴⁴	1998-2002	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Hospital-wide	All-cause mortality (28 day)	Risk factors for mortality & treatment outcome of ESBL-EC- and ESBL-KP-BSI	EC, KP
Raviv Y ⁴⁵	2004-2007	Israel	Cohort study, retrospective	Control group: non-ESBL-infection, second control group: no infection	patients with lung transplantation	Not provided	All-cause mortality (28 day)	Outcomes of lung transplant recipients infected by CRKP and ESBL carbapenem-sensitive KP (referred to MDR-KP)	KP
Kim HJ ¹¹	2005-2010	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Medical ward	All-cause mortality (28 day), LOS	Clinical outcome of patients with biliary tract infection: ESBL-producing bacterial isolates vs. non-ESBL-producing-bacterial isolates, predictors of poor prognosis, impact of ineffective antimicrobial therapy on clinical outcome	EC, KP
MacVane SH ⁴⁶	2011-2012	USA	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS	clinical & economic outcomes of patients with ESBL-EC- and ESBL-KP-UTI vs. non-ESBL-EC- and non-ESBL-KP-UTI	EC, KP
Abhilash KP ⁴⁷	2007	India	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Prevalence & risk factors & outcome of antibiotic treatment among hospitalised patients with ESBL-EC- and ESBL-Ks-BSI	GNB
Shanthi M ⁴⁸	2006	India	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Prevalence & impact on clinical outcome of ESBL-production among nosocomial isolates of EC & KP	EC, KP
Han SB ⁴⁹	2009-2013	South Korea	Cohort study, retrospective	Non-ESBL-infection	Children (immunocompromised, with cancer, neutropenic fever)	Pediatric ward	Attributable mortality, all-cause mortality (28 day)	Clinical outcomes of ESBL-EC- and ESBL-KP-bacteraemia & their antibiotic susceptibilities	EC, KP
Lee S ⁵⁰	2009-2011	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients with Acute Pyelonephritis	Entire hospital	All-cause mortality (14 day), LOS	Impact of ESBL on clinical outcomes of Acute Pyelonephritis treated with empirical ceftriaxone (which was inappropriate for ESBL-producing organisms)	EC
Artero A ⁶⁸	2013-2015	Spain	Cohort study, prospective	Non-ESBL-infection	Elderly	Medical ward	All-cause mortality, LOS	Identify clinical factors to predict ESBL-EC among elderly patients with UTI admitted to hospital in a high rate setting of ESBL-EC	EC

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Chen IL ⁶⁹	2004-2015	Taiwan	Cohort study, retrospective	Non-ESBL-infection	Neonates	Neonatal ward	All-cause mortality	Compare the clinical characteristics & laboratory data of preterm babies with EC BSI: survival vs. nonsurvival groups, ESBL vs non-ESBL groups, determine the predictive factors of EC BSI in preterm babies	EC
Islas-Munoz B ⁷⁰	2016-2017	Mexico	Cohort study, prospective	Non-ESBL-infection	Cancer patients	Oncologic ward	All-cause mortality (28 day)	Evaluate the clinical epidemiological characteristics & risk factors associated with mortality in cancer patients with BSI-special emphasis on MDR bacteria	GNB (and others)
Ma J ⁷¹	2012-2015		Cohort study, retrospective	Non-ESBL-infection	Patients with hematological diseases	Entire hospital	All-cause mortality (28 day)	Evaluate the antimicrobial resistance & clinical features & risk factors for septic shock & death of nosocomial EC-BSI	EC
Man MY ⁷²	2009-2016	China	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients, except patients from Burn unit, transplant surgery ward or with thoracic therapy	Entire hospital	All-cause mortality (28 day)	Evaluate the incidence & clinical characteristics & outcomes of patients with KP BSI in critical care & general ward settings	KP
Marando R ⁷³	2016	Tanzania	Cohort study, prospective	Non-ESBL-infection	Neonates	NICU	All-cause mortality	Investigate factors associated with ESBL-PE neonatal sepsis & mortality among neonates, characterise selected isolates to show virulence potential & transmission dynamics	GNB
Namikawa H ⁷⁴	2011-2015	Japan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Investigate clinical characteristics of patients with ESBL-EC-BSI	EC
Shi SH ⁷⁵	2008-2015	China	Cohort study, retrospective	Non-ESBL-infection	Patients with pyogenic liver abscess	Centre for hepatopancreaticobiliary diseases	All-cause mortality, LOS	Aetiology & morbidity & clinical characteristics of pyogenic liver abscess caused by ESBL-PE	GN
Tanir Basaranoglu S ⁷⁶	2011-2015	Turkey	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality (28 day)	Assess risk factors for health care associated ESBL-KP-BSI in children, analyze clinical outcomes: ESBL-KP vs. non-ESBL-KP	KP
Bazazi K ⁷⁷	2009-2015	France	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality, LOS, ICU-LOS	Determine, among ESBL-PE carriers, the prevalence & associated factors & clinical impact of ESBL-PE pneumonia, determine factors associated with ICUAP caused by carbapenem-resistant bacteria	GNB

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Ray S ⁷⁸	2014-2016	India	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Investigate spectrum of microbial resistance pattern in the community and their effects on mortality	GNB
Haruki Y ⁷⁹	2006-2016	Japan	Cohort study, retrospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Compare the clinical characteristics & outcomes of critically ill patients in an ICU, who were hospitalised for BSI caused by ESBL-EC or non-ESBL-EC.	GNB
Lin WT ⁸⁰	2009-2014	Taiwan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Investigate the clinical manifestations & bacteriological features of culture-proven, GNB arthritis	GNB
Guys H ⁸¹	2006-2011	South Africa	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality	Describe the clinical presentation of KPBSI, risk factors associated with ESBL-KPBSI, antibiotic susceptibility patterns of the KP isolates & KPBSI mortality including factors associated with in-patient mortality	KP
Lee CC ⁸²	2008-2013	Taiwan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Emergency Department	Attributable mortality, all-cause mortality (28 day), LOS, ICU-LOS	Analyse the impact of ESBL-producing isolates on the outcome of bacteremic patient after controlling for baseline patient characteristics & bacteraemia severity by using a propensity-matched analysis (PSM)	GNB
Huang YY ⁸³	2011-2013	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Determine cumulative incidence of ESBL urosepsis, identify major risk factors for ESBL urosepsis, determine impact of international travel on development of ESBL urosepsis	EC, KP
Komatsu Y ⁸⁴	2008-2013	Japan	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Identify risk factors & clinical outcomes in patients with BSI due to ESBL- or carbapenemase-producing EC, determine prevalence & genetic background	EC
Liu MM ⁸⁵	2011-2016	China	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	ICU-patients	ICU	All-cause mortality	Identify risk factors for ESBL-producing ECBSI among carriers at ICU	EC
Nivesvivat T ⁸⁶	2010-2017	Thailand	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality, LOS	Determine prevalence, risk factors & clinical outcomes of ESBL-producing EB in paediatric BSI	EC, KP

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Cordery RJ ⁸⁷	2004-2006	UK	Cohort study, retrospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Elucidate specific risk factors for the acquisition of ESBL infection in the ICU; all-cause mortality (in ICU) compared in patients with infections due to ESBL- and non-ESBL-producing organisms	GNB
Paikos GL ⁸⁸	2003-2005	Greece	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Identify risk factors associated BSI caused by integron-carrying EB; evaluate the consequences of these genetic elements on patient outcome	GNB
Gudiol C ⁸⁹	2006-2008	Spain	Cohort study, prospective	Non-ESBL-infection	Cancer patients and hematopoietic stem cell transplant patients	Entire hospital	All-cause mortality	Assess clinical features, risk factors, molecular epidemiology & outcome of ESBLEC BSI in hospitalised cancer patients	EC
Marchaim D ⁹⁰	2006-2008	Israel	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Define predictors & outcomes of ESBL BSI among patients with bacteraemia due to EB upon hospital admission	GNB
Menashe G ⁹¹	1997	Israel	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Determine: prevalence of ESBL-P organisms among adult patients with nosocomial EB BSI treated in our institution; association between ESBL production & resistance to other antibiotics; clinical characteristics of patients with nosocomial ESBL-P BSI compared with those infected with non-producing strains; impact of ESBL production on outcome of patients with nosocomial EB BSI	GNB
Ortega M ⁹²	1991-2007	Spain	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Describe source, resistance rate to fluoroquinolone & beta-lactam antibiotics and mortality of EC BSI episodes in a single institution; identify predictive factors for isolation of fluoroquinolone-resistant or ESBL- producing strains.	EC
Sziglyi M ⁹³	2005-2008	Hungary	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality,	Investigate risk factors for & outcomes of BSI caused by ESBL-producing and ESBL-non-producing KP	KP
Tsai SS ⁹⁴	2005-2006	Taiwan	Cohort study, retrospective	Non-ESBL-infection	Diabetic patients	Entire hospital	All-cause mortality	Analyze characteristics, risk factors & outcomes of diabetic patients with community- vs. hospital-acquired KP BSI	KP

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EC = *Escherichia coli*
KP = *Klebsiella pneumoniae*
GNB = Gram-negative bacteria
BSI = Bloodstream infection
UTI = Urinary tract infection
ICU = Intensive care unit
NICU = Neonatal intensive care unit
ESBL-PE = Extended-spectrum beta-lactamase-producing Enterobacteriaceae
EB = Enterobacteriaceae
LOS = Length of stay

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Supplementary table S5: Risk of bias assessment of case cohort studies according to Newcastle - Ottawa quality assessment scale:

Assessment criteria / Study author	1. Is the case definition adequate?	2. Representativeness of the cases:	3. Selection of Controls	4. Definition of Controls	5. Comparability of cases and controls on the basis of the design or analysis	6. Ascertainment of exposure	7. Same method of ascertainment for cases and controls	8. Non-Response rate
Lautenbach, E.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Apisarntharak, A.	Green	Green	Yellow	Green	Green	Green	Green	Green
Briongos-Figuero, L-S.	Green	Green	Yellow	Yellow	Grey	Green	Green	Green
Stone, P.W.	Green	Green	Brown	Yellow	Grey	Green	Green	Green
Kola, A.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Tsai, M.H.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Maslikowska, J.A.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Nguyen, M. L.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Denis, B.	Green	Green	Yellow	Green	Yellow	Green	Green	Green
Chopra, T.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Skippen, I.	Green	Green	Yellow	Yellow	Yellow	Green	Grey	Green
Apisarntharak, A.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Tumbarello, M.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Apisarntharak, A.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Kanafani, Z. A.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Zaoutis, T. E.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Song, K. H.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Kang, C. I.	Green	Green	Yellow	Yellow	Grey	Green	Green	Green
Rodriguez-Bano, J.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Lin, J. N.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Ku, N. S.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Kang, C. I.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Huang, Y. Y.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Komatsu, Y.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Liu, M. M.	Green	Green	Yellow	Green	Yellow	Green	Green	Green

Risk of bias assessment of cohort studies according to Newcastle - Ottawa quality assessment scale:

Study author / Assessment criteria	1. Representativeness of exposed cohort	2. Selection of non-exposed cohort	3. Ascertainment of exposure	4. Demonstration that outcome of interest not present at start	5. Comparability based on design or analysis	6. Assessment of outcome	7. Follow-up long enough for outcome	8. Adequacy of follow up of cohorts
Jean, S.S.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
Bhavnani, S. M.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Blomberg, B.	Yellow	Green	Green	Green	Grey	Yellow	Green	Green
Pena, C.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Onken, A.	Green	Green	Green	Green	Grey	Yellow	Green	Green
Melzer, M.	Green	Green	Green	Green	Grey	Yellow	Green	Green
Bennet, J.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Wu, Y.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Abhilash, K.	Green	Green	Green	Green	Green	Yellow	Yellow	Green
Artero, A.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Islas-Munos, B.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Marando, R.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Razazi, K.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Ray, S.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Panhotra, B.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Kim, S.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Chayakulkeeree, M.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Apisarnthanarak, A.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Ha, Y.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Du, B	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Pillay, T.	Yellow	Green	Green	Green	Grey	Yellow	Green	Green
Kim, B.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Kim, Y	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Marra, A.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Schwaber, M.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Leistner, R.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Loh, L.C.	Green	Green	Green	Green	Green	Yellow	Green	Red
Trecarichi, E.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Tuon, F.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Kang, C. I.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Pena, C.	Green	Green	Green	Green	Grey	Yellow	Green	Green
Tumbarello, M.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Gurntke, S.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Oh, M.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Leistner, R.	Green	Green	Green	Green	Grey	Yellow	Green	Green
Anunnatsiri	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green

1	Raviv, Y.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
2	Kim, H.J.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
3	MacVane, S.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
4	Shanthi	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
5	Han, S.B.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
6	Han, S.B.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
7	Lee, S.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
8	Chen, I-L.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
9	Ma, J.	Green	Green	Green	Green	Green	Yellow	Green	Green
10	Ma, J.	Green	Green	Green	Green	Green	Yellow	Green	Green
11	Man, M.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
12	Namikawa, H.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
13	Namikawa, H.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
14	Shi, S.	Yellow	Green	Green	Green	Grey	Yellow	Green	Green
15	Tanir Basarangolu, S.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
16	Tanir Basarangolu, S.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
17	Haruki, Y.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
18	Lin, W.	Green	Green	Green	Green	Grey	Yellow	Green	Green
19	Lin, W.	Green	Green	Green	Green	Green	Yellow	Green	Green
20	Buys, H.	Green	Green	Green	Green	Green	Yellow	Green	Green
21	Lee, C.C.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
22	Lee, C.C.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
23	Nivesvivat, T.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
24	Nivesvivat, T.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
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Supplementary table S6: Source of heterogeneity among effect estimates in studies on ESBL bloodstream infections in comparison with patients with non-ESBL bloodstream infections assessed using univariate meta-regression:

Subgroups / Outcome	All-cause mortality	Length of Stay
Mortality time	0.85	-
Pathogen	0.45	0.34
Study design	0.51	0.21
Study country	0.22	0.09
Income classification	0.17	0.80
Study period	0.57	0.78
Study setting: ICU ward	0.78	0.97
Study setting: Neonatal ward	0.62	0.97
Study setting: Pediatric ward	0.96	0.96
Study population: ICU patients	1.00	-
Study population: Children	0.96	0.96
Study population: Neonates	0.62	0.97
Information about therapy	0.53	
Appropriateness of therapy reported	0.68	
Information about outcome of therapy	0.74	-
MIC reported	0.28	-



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	5,6



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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	suppl.material
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8 and suppl. material
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	suppl.material
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8 and suppl. material
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7,8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9-10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9-10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11



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BMJ Open

Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria producing extended-spectrum beta-lactamases: a systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-030266.R2
Article Type:	Original research
Date Submitted by the Author:	13-Nov-2019
Complete List of Authors:	Shamsrizi, Parichehr; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease Gladstone, Beryl Primrose ; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease Carrara, Elena; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health Luise, Dora; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health Cona, Andrea; ASST Santi Paolo e Carlo, Clinic of Infectious and Tropical Diseases, Department of Health Sciences Bovo, Chiara; Integrated University Hospital of Verona, Medical Direction Tacconelli, Evelina; University Hospital Tubingen Department of Internal Medicine I Gastroenterology Hepatology and Infectious Diseases, Division of Infectious Disease; Integrated University Hospital of Verona, Division of Infectious Disease, Department of Diagnostic and Public Health
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases, Epidemiology
Keywords:	Extended-spectrum beta-lactamase, mortality, bloodstream infection, length of stay, meta-analysis, systematic review

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Manuscripts

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3 1 **Variation of effect estimates in the analysis of mortality and length of hospital stay in**
4 **patients with infections caused by bacteria producing extended-spectrum beta-**
5 **lactamases: a systematic review and meta-analysis**
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1 **ABSTRACT**

2 **Objective** To assess the variation of effect estimates in the analysis of mortality and length of
3 stay (LOS) in patients with infections caused by extended-spectrum beta-lactamase (ESBL)-
4 producing *Enterobacteriaceae*.

5 **Design** Systematic review and meta-analysis

6 **Methods** Literature search for clinical studies from 1 January 1960 to 1 October 2018 was
7 conducted in PubMed. Primary outcomes were risk ratios (RRs) of all-cause and attributable
8 mortality and weighted mean differences (WMDs) in LOS in patients with bloodstream
9 infections (BSIs) and non-invasive infections. Any change in the effect estimates was
10 assessed by grouping studies according to design, setting, economy-based country
11 classification, reporting period, microbiological aetiology, infection type, and adjustment for
12 appropriateness of empirical treatment. The impact of ESBL production was calculated using
13 random effect meta-analysis and heterogeneity was evaluated by I^2 statistics and
14 metaregression.

15 **Results** Eighty-four studies including 22,030 patients and 149 outcome measures were
16 included in the meta-analysis. Most studies were retrospective cohorts from high-income
17 countries, providing unadjusted estimates. ESBL production in patients with BSIs (56 studies)
18 increased the RR for all-cause mortality by a factor of 1.70 (95% CI: 1.52-1.90; $p < 0.001$),
19 attributable mortality (16 studies) by 1.75 (95% CI: 1.448-2.108; $p < 0.001$), and WMD in the
20 intensive care unit by 3.07 days (95% CI: 1.61-4.54; $p < 0.001$). WMD in hospital LOS was
21 significantly higher in BSIs (4.41 days; 95% CI: 3.37-5.46; $p < 0.001$) and non-invasive (2.19
22 days; 95% CI: 1.56-2.81; $p < 0.001$). Subgroup analyses showed variation of estimates by
23 study design, population, strain, and assessment of appropriateness of empiric treatment. High
24 heterogeneity was observed in all analyses.

25 **Conclusions** Current evidence of the clinical burden of infections caused by ESBL-producing
26 bacteria is highly heterogeneous and based mainly on unadjusted estimates derived from
27 retrospective studies. Despite these limitations, ESBL production in strains causing BSIs
28 seems associated with higher all-cause and attributable mortality and longer hospitalisation.

29 **KEYWORDS**

30 Extended-spectrum beta-lactamase, mortality, bloodstream infection, length of stay, meta-
31 analysis, systematic review
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1 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 2 ▶ Evidence of the impact of ESBL production on mortality and length of stay in strains
- 3 causing bacteremic and non-bacteremic infections was collected systematically.
- 4 ▶ Effect of multiple epidemiological and clinical variables was assessed in the calculation of
- 5 estimates.
- 6 ▶ Heterogeneity among studies was assessed.
- 7 ▶ Only few studies had been performed in high-risk populations or low-income countries.

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1 INTRODUCTION

2 Infections caused by extended-spectrum beta-lactamase (ESBL)-producing
3 *Enterobacteriaceae* are responsible for high morbidity and mortality worldwide.^{1,2,3} The 2018
4 World Health Organization list of antibiotic-resistant pathogens identified mortality as the
5 most important criteria to prioritise bacteria for research and development of new, effective
6 antibiotics.¹ In this prioritisation exercise, ESBL-producing *Enterobacteriaceae* were
7 designated a critical priority because of their high all-cause mortality and high prevalence
8 globally in healthcare-associated and community-acquired infections. The incidence and
9 attributable mortality of multidrug-resistant bacterial infections, including ESBL-producing
10 *Enterobacteriaceae*, in European countries has been recently estimated using a modelling
11 analysis.⁴ In 2015 ESBL-producing *Escherichia coli* was responsible for almost 300,000
12 infections in Europe and 9,000 attributable deaths, and ESBL-producing *Klebsiella*
13 *pneumoniae* caused around 70,000 infections and more than 3,500 deaths. The major
14 limitation of this analysis is the sparseness of evidence on mortality due to ESBL-producing
15 bacteria, which was limited largely to studies conducted in high-income countries.

16 Two systematic reviews have been performed to define the impact of ESBL production on
17 mortality due to *Enterobacteriaceae*.^{2,3} Both meta-analyses included studies targeting
18 bloodstream infections (BSIs) and showed doubling all-cause mortality for ESBL-associated
19 bacteraemia compared to non-ESBL *Enterobacteriaceae* bacteraemia. A major drawback of
20 the analyses, highlighted by the authors, was the lack of control for confounding and limited
21 adjustment for empiric therapy. No systematic review has been performed to assess
22 attributable mortality and other indicators of clinical impact such as length of stay (LOS).

23 Because estimates of clinical burden drive policy design for antibiotic stewardship and
24 infection control interventions, precise and current estimates are essential. The objective of
25 this systematic review and meta-analysis was to assess the variation of effect estimates in the
26 analysis of mortality and LOS in patients with infections due to ESBL-producing
27 *Enterobacteriaceae*.

28 METHODS

29 Literature search strategy

30 The search was performed by 2 researchers (BPG and PS) in PubMed on 05 October 2018
31 using search terms (supplementary table S1) relevant to the following combinations: (ESBL
32 AND *Escherichia coli* AND mortality) OR (ESBL AND *Klebsiella pneumoniae* AND
33

1 mortality) OR (ESBL AND Escherichia coli AND length of stay OR length of hospitalisation)
2 OR (ESBL AND Klebsiella pneumoniae AND length of stay OR length of hospitalisation).
3 Reference lists of retrieved articles were also searched.

4 **Eligibility criteria**

5 We included all clinical studies with a comparison group assessing all-cause mortality,
6 attributable mortality, and overall LOS and intensive care unit stay (ICU) LOS in hospitalised
7 patients with ESBL infections. Studies published from 1 January 1960 to 1 October 2018
8 irrespective of the clinical setting and study design were included. No language restriction has
9 been applied. Diagnostic studies, reviews, case reports, non-clinical studies, and abstracts of
10 conference presentations were not included.

11 **Data extraction**

12 Two reviewers (PS and BPG) independently assessed the eligibility of trials and extracted
13 data. In case of disagreement, a third reviewer (DL) was consulted. Extracted data were
14 collected in an electronic worksheet, using EpiInfo 7.1: authors, journal, country, year of
15 publication, year of study, time of data collection, study design, comparison group, study
16 setting, population, aetiology, type and site of infection, and raw data related to mortality and
17 LOS/ICU-LOS. Countries were classified as high-, middle-, or low-income using the World
18 Bank Atlas method.⁵ Adjusted effect estimates such as odds ratios (ORs) or hazard ratios and
19 quality indicators such as reporting of antibiotic therapy, appropriateness of empirical
20 treatment, resistance mechanisms, and minimum inhibitory concentrations (MICs) were also
21 extracted.

22 Mortality data were extracted as all-cause mortality or attributable mortality as defined in the
23 studies. Where available, prespecified time periods for mortality assessment (i.e., 14 days, 28
24 days, in-hospital) were also extracted. LOS and ICU-LOS were extracted as days with mean
25 and standard deviation or median and interquartile range.

26 **Data analysis**

27 The primary outcomes for the clinical impact of ESBL infections were RRs of all-cause and
28 attributable mortality and the weighted mean difference (WMD) in LOS and ICU-LOS in
29 patients with ESBL infections compared with those in patients with non-ESBL infections and,
30 where available, with uninfected patients. The impact of ESBL production on attributable and
31 all-cause mortality was calculated with random effect meta-analysis and expressed as RR with

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3 1 95% confidence interval (CI). WMD in days with 95% CI was calculated to express the
4 2 excess in LOS and ICU-LOS.

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7 3 Variation of the effect estimate was assessed by grouping the studies according to the
8 4 following study/outcome characteristics: mortality time assessment (7 vs 14 days), aetiology
9 5 (*E. coli* vs *K. pneumoniae*), infection localisation, clinical setting (paediatric, oncology, ICU),
10 6 economic country areas (high-income countries [HICs] vs low- and medium-income countries
11 7 [LMICs]), study design, assessment of empiric therapy, and year. Studies were classified
12 8 according to the type of infections evaluated. Studies on BSIs were defined as those in which
13 9 patients had positive blood cultures and were admitted to the hospitals with signs and
14 10 symptoms of systemic inflammatory response and requiring therapy, similarly to the
15 11 definition adopted by the most recent cohort studies on ESBL infections.⁶ Non-invasive
16 12 infections included non-bacteremic patients with only localised signs and symptoms of
17 13 infection (such as urinary tract infections or superficial surgical site infections).

18
19 14 Subgroup analysis was computed only if more than 2 studies were available for each group.
20 15 Heterogeneity was evaluated by using I^2 statistics and metaregression. Overall significance
21 16 testing was carried out using Wald tests adjusted using the Bonferroni correction. The
22 17 unadjusted ORs were compared with the adjusted ORs to estimate the effect of adjustment.
23 18 Reporting and publication bias was presented in funnel plots (supplementary figure 1 and 2)
24 19 and tested by Egger's test. Statistical analyses were performed using Stata version 15. Risk of
25 20 bias was assessed independently by two authors (PS, DL) using the Newcastle - Ottawa
26 21 quality assessment scale for cohort studies.⁷ Studies were classified as low, moderate, or
27 22 high quality according to AHRQ standards (supplementary table S2). All meta-analyses
28 23 were performed in accordance with the Cochrane Collaboration recommendations⁸ and
29 24 reported according to the PRISMA statement.⁹

30 25 The protocol is available online.
31 26 ([https://im1-tuebingen.de/wp-](https://im1-tuebingen.de/wp-content/uploads/2019/03/ClinicalImpactAMR_SR_studyprotocol_2018.pdf)
32 27 [content/uploads/2019/03/ClinicalImpactAMR_SR_studyprotocol_2018.pdf](https://im1-tuebingen.de/wp-content/uploads/2019/03/ClinicalImpactAMR_SR_studyprotocol_2018.pdf))

33 28 **Patient and Public Involvement**

34 29 There was no patient or public involvement in this systematic review of published literature.

35 30 **RESULTS**

36 31 Our literature search identified 1006 studies, and 92 (9.2%) met the eligibility criteria on the
37 32 basis of abstract screening. Full-text screening excluded an additional 5 articles, providing an

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3 1 evidence base of 87 studies (Figure 1).¹⁰⁻⁹⁶ The 87 studies included in the qualitative analysis
4 were conducted between 1991 and 2017 in 25 countries, mainly in South Korea (14 studies),
5 2 Thailand (7), USA (7), Taiwan (7), and Spain (7). Sixty (68.9%) studies were performed in
6 3 HICs, 26 (29.9%) in LMICs, and 1 included both HICs and LMICs.⁵⁶ About half (44, 50.6%)
7 4 were retrospective cohort studies, 24 (27.6%) case cohort studies, and 18 (20.7%) prospective
8 5 cohort studies; 1 study had an interventional design.⁵⁷ The comparison group was patients
9 6 with infections caused by gram-negative non-ESBL producers in 82 (94.3%) studies, non-
10 7 infected patients in 2 (2.3%), and both control groups in 3 (3.5%). Most (57, 65.5%) studies
11 8 included data from the entire hospital, while a few focused on specific settings, mainly ICUs
12 9 (9, 10.3%) and paediatric wards (8, 9.2%). The most common ESBL-producing bacteria were
13 10 *E. coli* (23, 26.4%) and *K. pneumoniae* (17, 19.5%). An overview of study characteristics is
14 11 provided in online supplementary table S3.
15 12

16 13 Because data in 3 studies^{22,61,87} were insufficient for quantitative analysis, 84 (96.6%) studies
17 14 were included in the meta-analysis analysing data from 22,030 patients and 149 outcome
18 15 measures. Fifty-seven studies analysed BSIs and 10 non-invasive infections. Study
19 16 characteristics for all studies are provided in online supplementary table S4. 49 (58.3%)
20 17 studies were of high quality, 23 (27.3%) were of moderate quality, and 12 (14.3%) were of
21 18 low quality (supplementary table S5).
22 19

20 19 **All-cause mortality**

21 20 All-cause mortality was reported in 81 studies including 21,942 patients (56 on BSIs and 7 on
22 21 non-invasive infections). ESBL production in patients with BSIs increased all-cause mortality
23 22 by a factor of 1.70 (95% CI: 1.52-1.90; $p<0.001$; $I^2=45.3%$; $p<0.001$) while studies including
24 23 non-invasive reported a RR of 1.58 (95% CI: 1.23-2.02; $p<0.001$) (supplementary figure 3).
25 24 Among the BSI patients, the RR increased over time from 1.56 (95% CI: 1.15-2.11; $p=0.004$)
26 25 in 1991-1999 to 1.74 (95% CI: 1.50-2.01; $p<0.001$) in 2000-2009, and it was stable in 2010-
27 26 2018 (1.72, 95% CI: 1.39-2.13; $p<0.001$). The RR was higher in studies assessing
28 27 appropriateness of empiric therapy (RR=1.75; 95% CI 1.54-1.99; $p<0.001$) than in those that
29 28 did not (RR=1.55; 95% CI 1.26-1.90; $p<0.001$). The subgroup analysis by pathogen showed
30 29 that ESBL production increased the RR in BSIs due to *E. coli* (RR=1.82; 95% CI: 1.50-2.21;
31 30 $p<0.001$) compared to those due to *K. pneumoniae* (RR=1.48; 95% CI: 1.17-1.87; $p=0.001$).
32 31 Stratification by population age showed a higher RR in paediatric population (RR=2.09; 95%
33 32 CI: 1.62-2.71; $p<0.001$). Effect estimates did not vary significantly by study country,
34 33 mortality time assessment (14 vs 28 days), ESBL molecular resistance mechanisms, or study

1 design (Figure 2 and online supplementary figure 4). Adjusted estimates for inappropriate
2 empirical antibiotic therapy were provided for 14 studies. The pooled unadjusted OR for all-
3 cause mortality was 2.91 (95% CI: 2.23-3.81; $p < 0.001$, $I^2 = 27.1\%$; $p = 0.164$) and the pooled
4 OR after adjusting for receipt of appropriate empirical treatment was 3.22 (95% CI: 1.53-
5 6.76; $p = 0.002$; $I^2 = 87.5\%$; $p < 0.001$). The impact of ESBL production on LOS and mortality
6 varied according to the infection type, with higher effect in intra-abdominal, respiratory and
7 BSIs (supplemental figure 5 and 6).

8 **Attributable mortality**

9 Attributable mortality was analysed in 16 studies including 2,885 patients. All studies were
10 performed in HICs. ESBL production in patients with BSIs increased the risk of attributable
11 mortality by a factor of 1.75 (95% CI: 1.45-2.11; $p < 0.001$; $I^2 = 0\%$; $p < 0.001$). The RR
12 increased over time from 1.53 (95% CI: 1.10-2.12; $p = 0.011$) in 1991-1999 to 1.91 (95% CI:
13 1.43-2.54; $p < 0.001$) in 2000-2009 (Figure 3). Pathogen-specific RR for attributable mortality
14 was 1.60 (95% CI: 1.18-2.15; $p = 0.002$) for *K. pneumoniae* and 1.76 (95% CI: 1.33-2.34;
15 $p < 0.001$) when the gram-negative organisms were analysed all together without species
16 differentiation. The subgroup analysis showed the RR was lower in case cohort studies (1.56;
17 95% CI: 1.09-2.25; $p = 0.016$) than in cohort studies (1.80; 95% CI: 1.37-2.37; $p < 0.001$).

18 **Length of stay**

19 LOS data were provided in 37 studies (17 on BSIs and 8 on non-invasive) analysing 38
20 outcome measures. The WMD of LOS in patients with BSIs was 4.41 days (95% CI: 3.37-
21 5.46; $p < 0.001$) and decreased from 5.72 days (95% CI: 2.69-8.75; $p < 0.001$) in 1991-1999 to
22 4.22 days (95% CI: 3.02-5.43; $p < 0.001$) in 2000-2009 and was stable up to 2018 (4.30 days;
23 95% CI: 1.38-7.22; $p = 0.004$). Higher WMD ($p < 0.001$) was observed for BSIs due to *K.*
24 *pneumoniae* (7.67 days; 4.63-10.71) than for those due to *E. coli* (6.07 days; 95% CI 3.71-
25 8.43). Retrospective cohort studies reported higher ($p < 0.001$) WMD (6.43 days; 95% CI:
26 4.66-8.21; $p < 0.001$) than case cohort studies (3.32 days; 95% CI: 2.03-4.61). Studies in HICs
27 showed higher WMD (4.56 days; 95% CI 3.43-5.70; $p < 0.001$) than studies in LMICs (3.55
28 days; 95% CI 0.84-6.26; $p = 0.01$) (Figure 4).

29 Studies with non-invasive infections reported a WMD of 2.19 days (95% CI: 1.56-2.81;
30 $p < 0.001$), which decreased from 7.66 (95% CI: 5.83-9.46; $p < 0.001$) in 2000-2009 to 1.44
31 (95% CI: 0.77-2.10; $p < 0.001$) in 2010-2018 (online supplementary figure 7).

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3 1 The data on ICU-LOS were provided in 7 studies and showed that BSIs caused by ESBL
4 2 producers had a WMD of LOS of 3.07 days (95% CI: 1.61-4.54; $p < 0.001$).

6
7 3 Heterogeneity of the studied effect-modifiers did not reach statistical significance when
8 4 assessed by metaregression (supplementary table S6). Sensitivity analysis based on the quality
9 5 of studies revealed no notable difference in the effect estimates after exclusion of low-quality
10 6 studies (data not shown). Egger's test and the funnel plots (online supplementary figure 1 and
11 7 2) showed evidence for small study effects ($p < 0.001$) and publication bias.

16 8 **DISCUSSION**

18 9 This systematic review shows that ESBL production has a significant impact on the most
19 10 relevant patient-related clinical outcomes. In the subgroup analyses, all-cause mortality,
20 11 attributable mortality, and LOS both in hospital and in ICU were higher for patients with BSIs
21 12 due to ESBL-producing *Enterobacteriaceae* than for patients with BSIs due to non-ESBL-
22 13 producing strains. Non-invasive infections caused by ESBL-producing strains were associated
23 14 with higher all-cause mortality and prolonged LOS. Within the limitation of the low number
24 15 of studies evaluating specific patient populations, paediatric and cancer patients seemed to
25 16 suffer a higher impact of ESBL invasive infections than the overall population. Stratifying by
26 17 pathogen type, the impact of ESBL production was higher for *E. coli* BSIs than for *K.*
27 18 *pneumoniae* BSIs. No relevant differences in mortality analysis emerged with stratification by
28 19 study design or country income level. Impact of ESBL infections on mortality became more
29 20 evident in more recent studies. Studies reporting on appropriateness of empirical therapy,
30 21 ESBL resistance mechanisms, and MICs showed a higher clinical impact of ESBL infections
31 22 than studies not assessing these variables. In particular, pooled ORs adjusted for inappropriate
32 23 empirical treatment, showed a remarkably higher OR for mortality in patients with ESBL
33 24 infections.

34 25 Our findings confirm the results of previous systematic reviews. Schwaber et al. performed a
35 26 systematic review comparing mortality in ESBL BSIs and non-ESBL BSIs in studies
36 27 published through 2003.² The authors show a pooled RR for all-cause mortality of 1.85 but, in
37 28 contrast to our study, they combined *E. coli*, *Klebsiella* spp., and *Proteus* spp. in the analysis
38 29 because of sample size limitations. Rottier et al. analysed studies published through 2010 and
39 30 adjusting results for inappropriate empirical treatment found an adjusted OR of 1.37.³ Our
40 31 study, adding more than 50 studies in 17 years to the Rottier systematic review, confirmed the
41 32 clinical importance of ESBL production to all-cause mortality and for the first time assessed
42 33 the role of ESBL production on attributable mortality. We addressed relevant effect-modifiers

1 through subgroup analyses and found that population, pathogen, and assessment of empiric
2 therapy all had an impact on estimates. Because we believe that appropriate empirical
3 treatment plays a relevant role in invasive infections, we performed a secondary analysis by
4 pooling only adjusted ORs and confirming the significant impact of antibiotic resistance as
5 already shown in a previously published systematic review.⁹⁷ The lack of consideration of
6 appropriateness of therapy in the studies evaluating mortality seems to underestimate the
7 impact of ESBL production on mortality. However, studies assessing the impact of
8 appropriate therapy did not provide homogeneous definition and could refer either to
9 empirical or definite therapy or a single component irrespective of the dosage, making results
10 difficult to interpret. Especially in infections with different sources and different clinical
11 severity, the sole contribution of empirical therapy remains challenging to measure. For
12 example, patients with UTI receiving inappropriate empirical antibiotic therapy can
13 potentially show a favourable outcome, most probably due to the high concentration of
14 antibiotic reached in the urinary tract.⁹⁸

15 Community acquired ESBL infections emerged in the late 1990s and show an increasing
16 trend.^{99,100} Recent study shows that community onset ESBL infections are associated with
17 lower mortality compared with healthcare associated and hospital acquired infections.¹⁰¹ The
18 place of acquisition could not be appropriately addressed in our meta-analysis due to the lack
19 of data in included studies.

20 Our systematic review contributes to the discussion on the limitation of current evidence for
21 the estimation of mortality due to antibiotic-resistant infections. The impact of ESBL
22 production on LOS in our study has shown that both BSIs and non-invasive infections lead to
23 prolongation of hospitalisation.

24
25 Our study has some limitations. Although results of the meta-analyses were significant in all
26 the subgroups, we could analyse only a limited number of studies providing information for
27 subgroups such as haematological patients and low-income countries, making generalizability
28 of results less certain for these specific patient populations. Only a few studies reported MIC
29 data or specific ESBL molecular resistant phenotype (i.e., AmpC). Moreover, publication bias
30 was detected in both the main analyses (all-cause mortality and LOS), thus implying the
31 possibility that results from small studies with non-significant results might have been
32 conducted and not published, resulting in a possible overestimation of our results. The non-
33 homogeneous reporting of some relevant data in published literature (e.g., disease severity,

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3 1 underlying comorbidities and resistance mechanism) may also have affected the precision of
4 2 the estimate. Patients with ESBL are intrinsically at higher risk of mortality and complications
5 3 because they are often older, have more comorbidities or higher antibiotic exposure, and are
6 4 at higher risk of receiving inappropriate empirical treatment.¹⁰² Finally, due to resource
7 5 constraints, we had to limit our search to PubMed database with the chance of missing
8 6 relevant studies.

9
10 7 In summary, our systematic review emphasises the importance of suspicion and confirmation
11 8 of ESBL production as soon as possible for invasive infections and demonstrates that ESBL
12 9 production increases the risk of attributable mortality and LOS in both hospital and ICU for
13 10 invasive and non-invasive infections. Patients with ESBL infections remain at higher risk of
14 11 mortality and prolonged LOS even after adjustment for empiric inappropriate treatment.
15 12 Control for other relevant effect-modifiers is hindered by the sparseness of published data.
16 13 Individual patient data (IPD) network meta-analyses are needed to define differences in
17 14 outcomes between severe intravascular infections and bacteremia. Future studies addressing
18 15 the clinical burden of drug-resistant infections must include ESBL production and should
19 16 assess both the impact of molecular mechanisms of resistance and effect on specific patient
20 17 populations such as haematological patients and those in LMIC.

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24 21 analysis. PS and AC extracted data and wrote the first draft of the manuscript. DL contributed
25 22 to the first draft of the manuscript. EC and ET wrote the final version of the manuscript. CB
26 23 reviewed the paper. All authors read, edited, and approved the final manuscript. The
27 24 corresponding author had full access to all the data in the study and had final responsibility
28 25 for the decision to submit for publication.

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35 32 **Patient consent** Not required

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1 **Data sharing statement** Requests for data should be addressed to the corresponding author.

2
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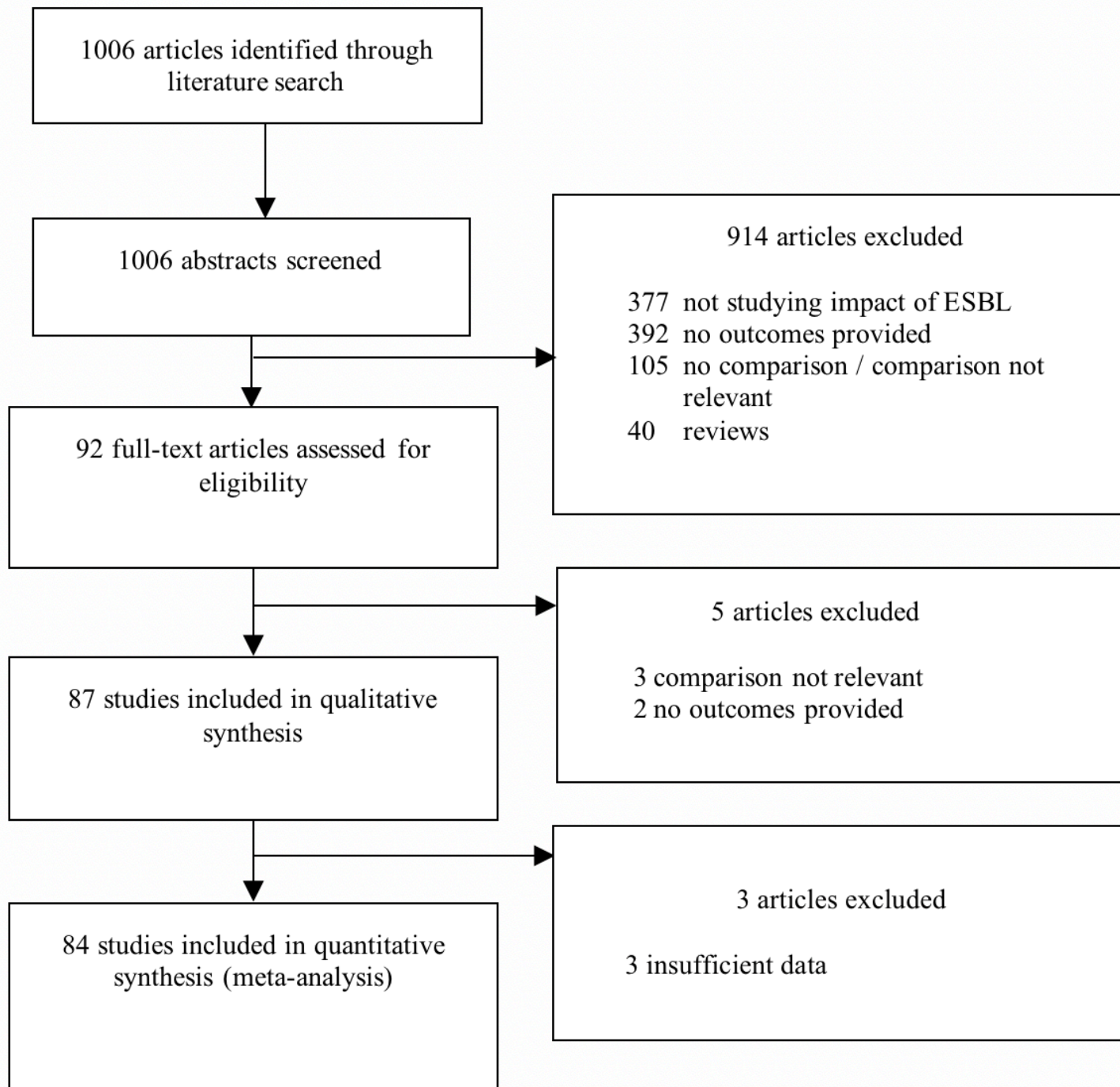
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3 **1 FIGURE LEGENDS**

4 2
5 3 Figure 1: Literature search and study inclusion and exclusion
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8 5 Figure 2: Pooled risk ratios for all-cause mortality in patients with ESBL bloodstream
9 6 infections compared to patients with non-ESBL bloodstream infections— subgroups not
10 7 included in attributable mortality
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12 9 Figure 3: Pooled risk ratios for attributable mortality in patients with ESBL bloodstream
13 10 infections compared to patients with non-ESBL bloodstream infections
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16 12 Figure 4: Weighted mean difference in the length of stay for patients with ESBL bloodstream
17 13 infections compared to patients with non-ESBL bloodstream infections
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risk
ratio (95% CI)

Category

N

Overall

Overall 56 1.70 (1.52, 1.90)

Mortality time

14 day mortality 5 1.77 (1.15, 2.72)

28 day mortality 22 1.63 (1.35, 1.97)

Time not defined 27 1.70 (1.47, 1.97)

Income classification

High income countries 41 1.76 (1.54, 2.00)

Low/middle income countries 15 1.56 (1.25, 1.96)

Study population

All kinds of patients 36 1.65 (1.43, 1.90)

Cancer patients 5 1.73 (1.16, 2.57)

Children 7 2.09 (1.62, 2.71)

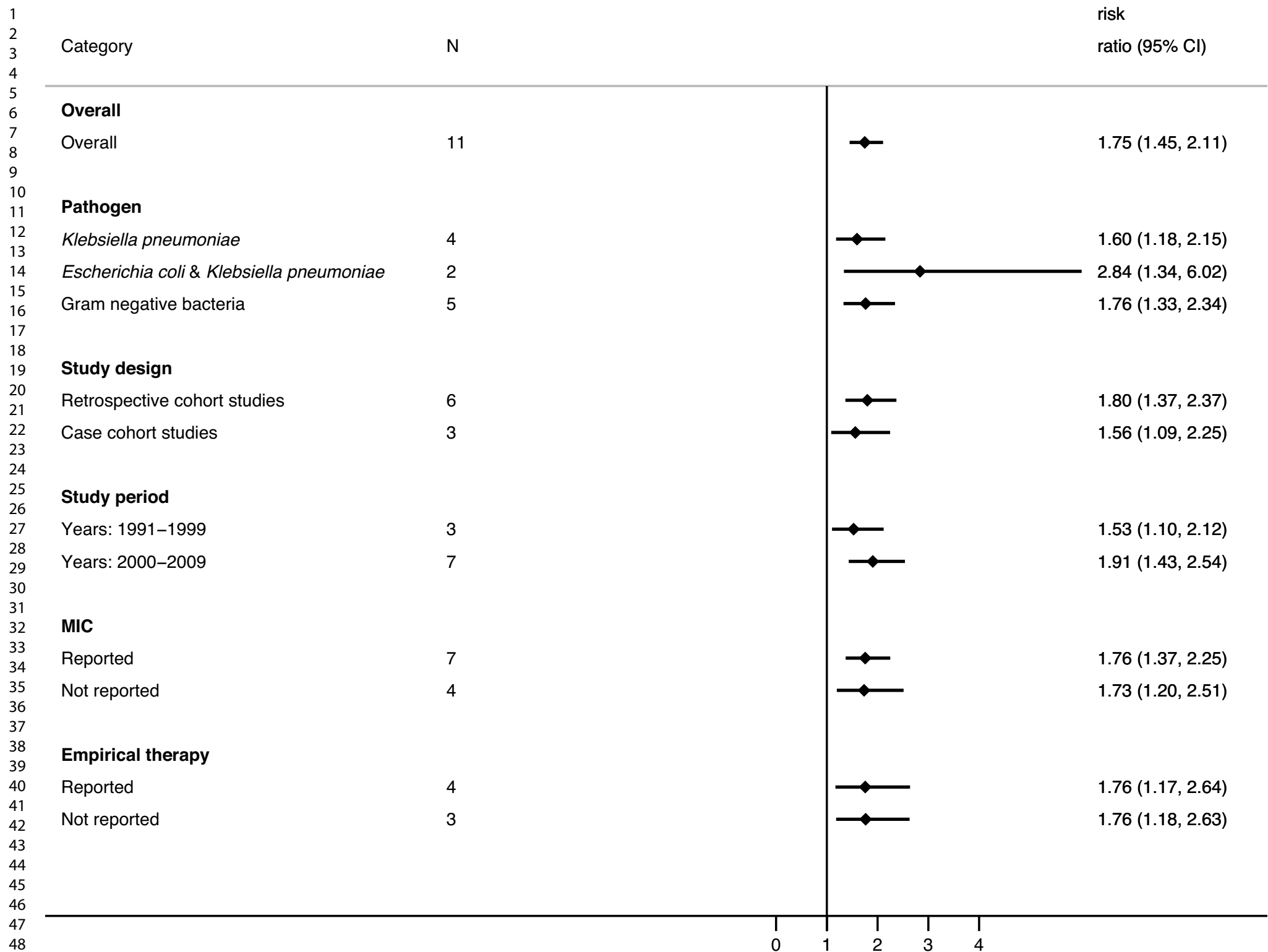
Neonates 3 1.76 (1.27, 2.45)

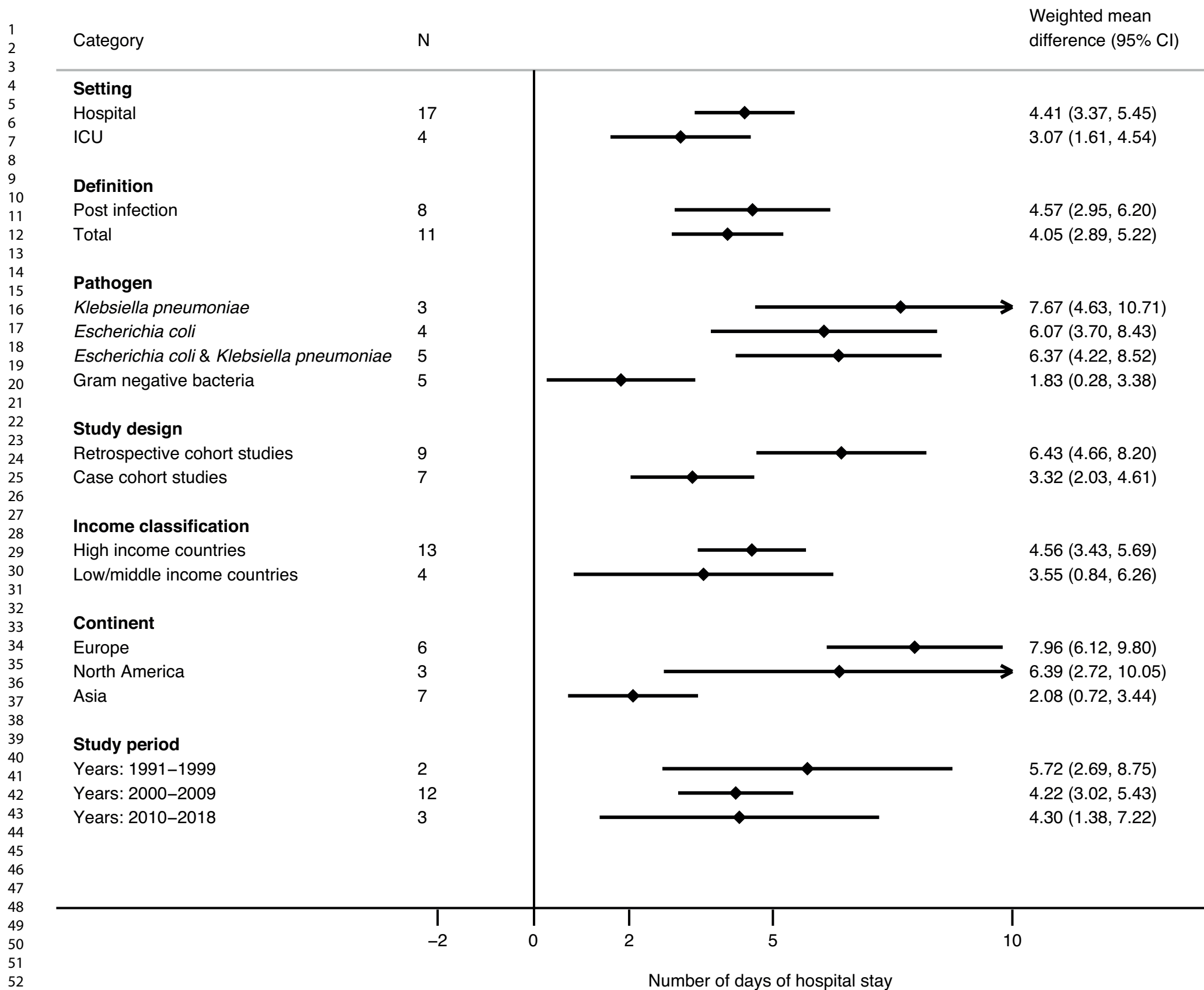
Appropriateness of therapy

Reported 44 1.75 (1.54, 1.99)

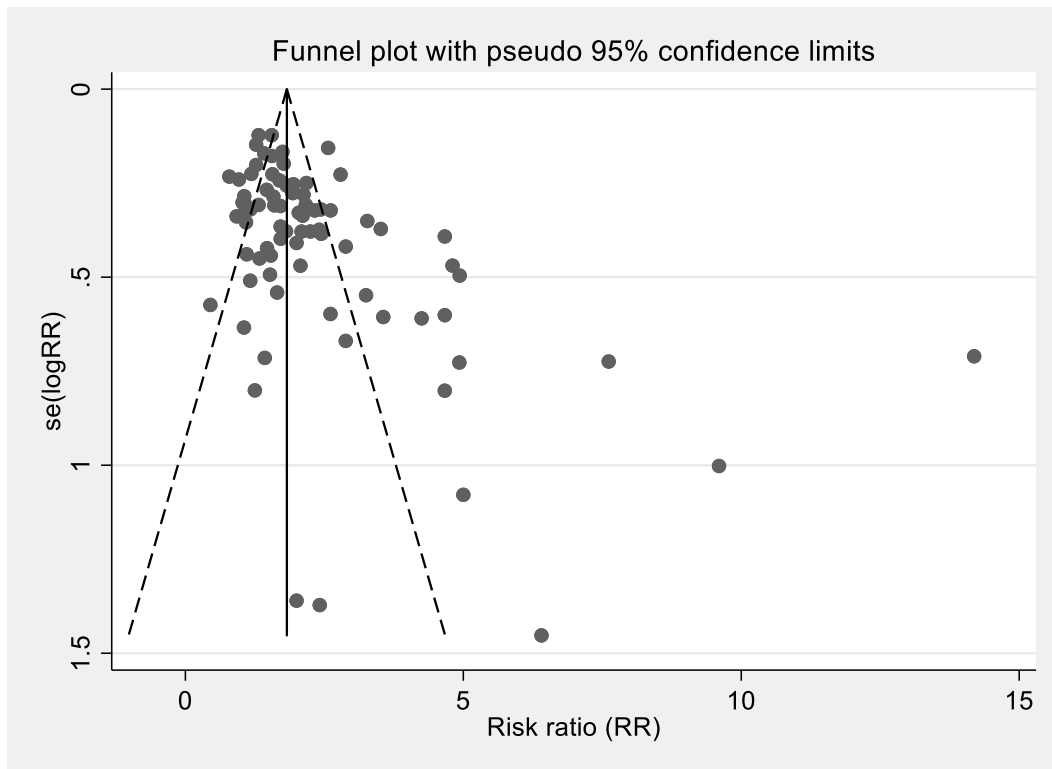
Not reported 12 1.55 (1.26, 1.90)

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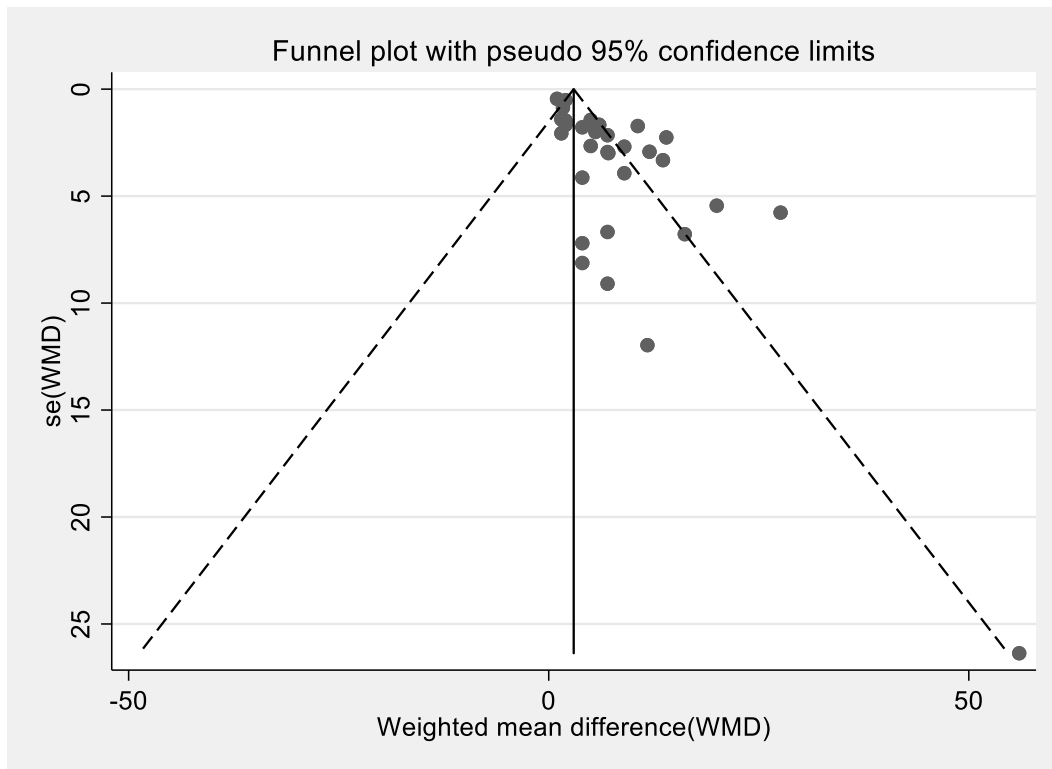


Supplementary figure 1: Funnel plot of risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections



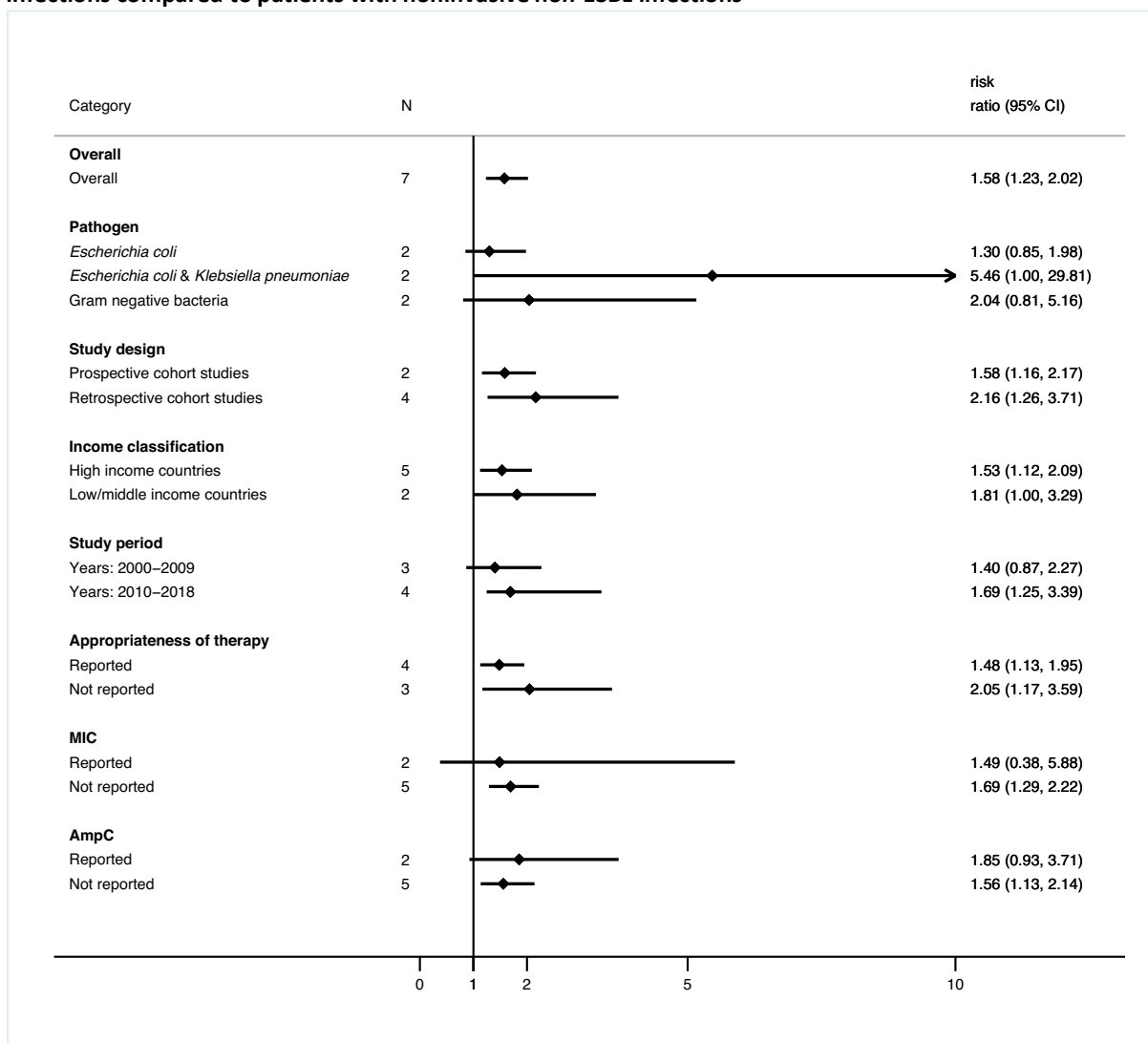
The y axis $se(\log RR)$ is the standard error of the log risk ratio. Pseudo 95% confidence limit refers to the 95% confidence limits around the summary treatment effect for each standard error on the vertical axis and to the expected distribution of studies in the absence of heterogeneity or of selection biases.

Supplementary figure 2: Funnel plot of weighted mean differences in the length of stay for patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections



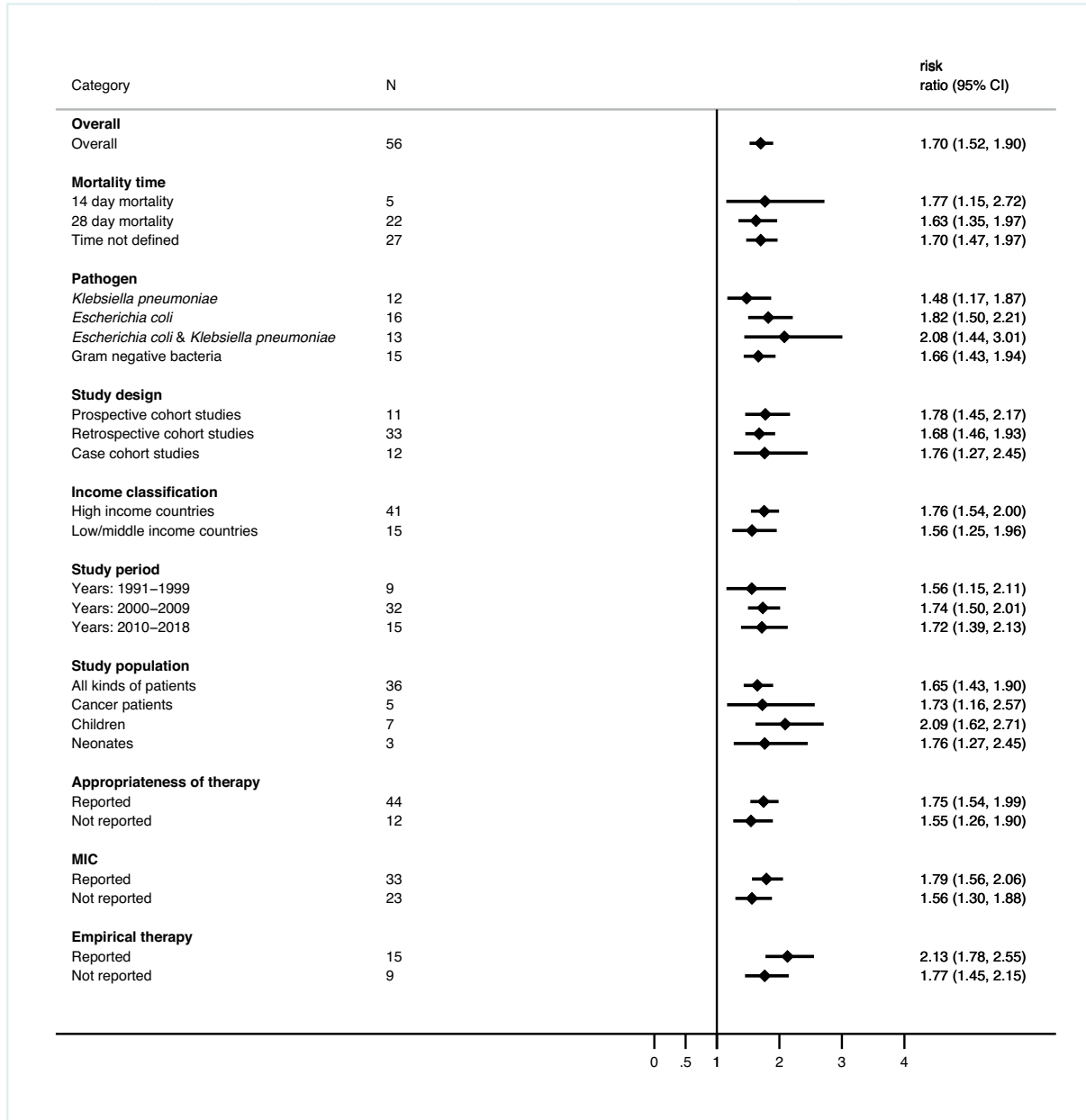
The y axis $se(WMD)$ is the standard error of the weighted mean difference. Pseudo 95% confidence limit refers to the 95% confidence limits around the summary treatment effect for each standard error on the vertical axis and to the expected distribution of studies in the absence of heterogeneity or of selection biases.

Supplementary figure 3: Pooled risk ratios for all-cause mortality in patients with noninvasive ESBL infections compared to patients with noninvasive non-ESBL infections

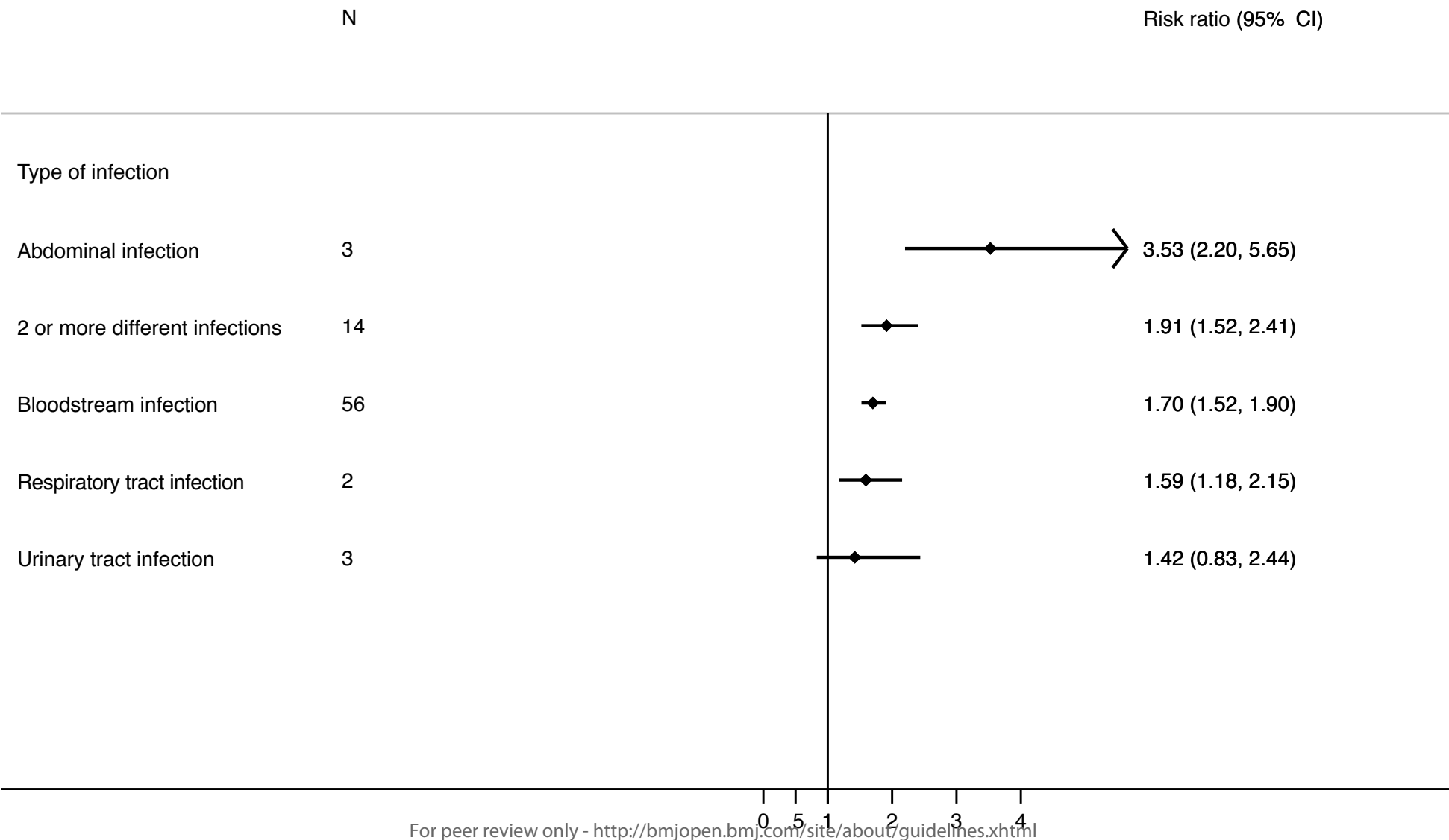


Only

Supplementary figure 4: Pooled risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections—all subgroups



Supplementary figure 5: Pooled risk ratios for all-cause mortality stratified by type of infection

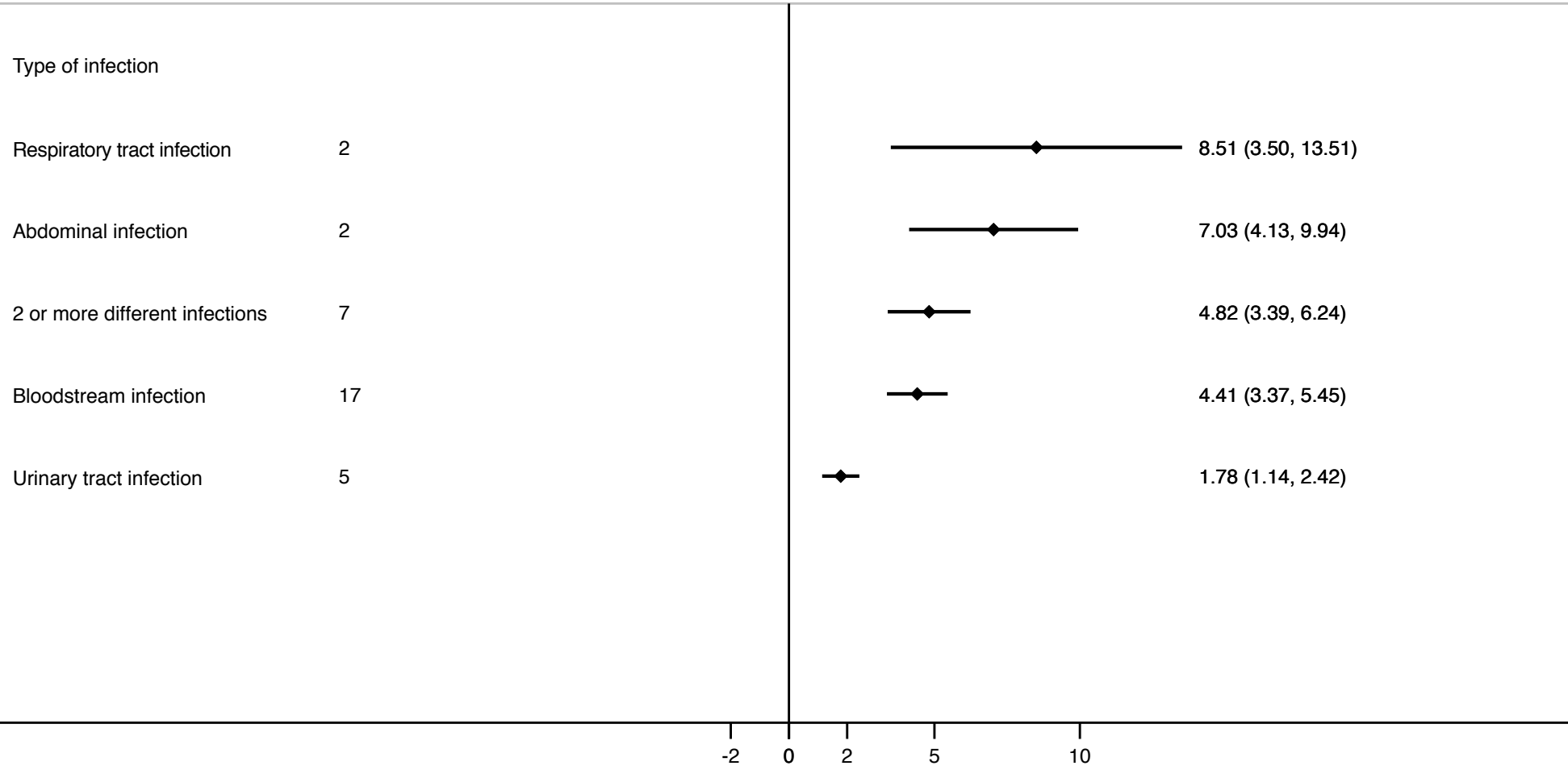


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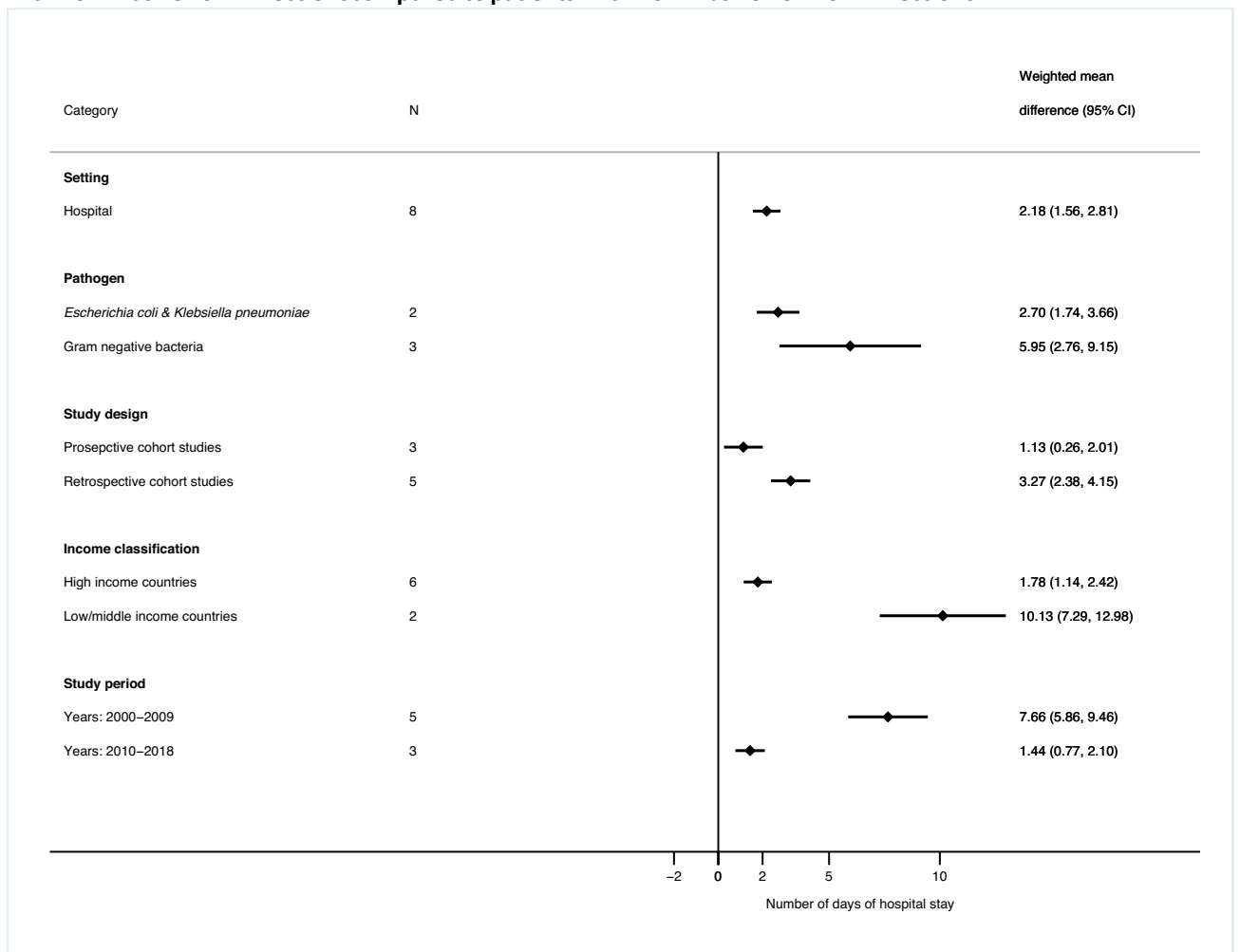
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Supplementary figure 6: Weighted mean differences in length of hospital stay stratified by type of infection

N Weighted mean difference (95% CI)



Supplementary figure 7: Weighted mean differences in length of hospital stay in patients with noninvasive ESBL infections compared to patients with noninvasive non-ESBL infections



Supplementary table S1: Search terms used in PubMed :

((ESBL[tw] OR ""Extended spectrum beta-lactamase""[tw] OR ESBL[Mesh] OR ""Extended spectrum beta-lactamase"" [Mesh]) OR Extended spectrum ? lactamase[tw] OR Extended spectrum ? lactamase[Mesh])

AND

(Escherichia Coli[Mesh] OR E.coli[Mesh] OR Escherichia Coli[tw] OR E.coli[tw])) OR (Klebsiella pneumoniae[Mesh] OR K.Pneumoniae[Mesh] OR Klebsiella pneumoniae[tw] OR K.Pneumoniae[tw])

Coupled with

(length of stay[mesh] OR (hospitalisation[tw] AND length[tw]) OR length of hospitalisation[tw] OR length of hospitalization[tw] OR duration of hospitalization[tw] duration of hospitalisation[tw] OR LOS[tw] OR ((period[tw] OR length[tw]) AND (hospital stay[tw] OR hospitalisation[tw] OR hospitalization[tw])) OR

(mortality[mesh] OR mortality[tw] OR death rate[tw] OR fatality[tw] OR survival rate[tw] OR death[tw] OR died[tw] OR dead[tw])) OR

(cost*[Title/Abstract] OR "costs and cost analysis"[MeSH:noexp])

Coupled with

("0001/01/01"[PDat] : "2018/10/01"[PDat])

Supplementary table S2: Modified Newcastle Ottawa quality assessment scale for case-control studies and cohort studies.

For case cohort studies, the quality criteria assessed are			
1	Is the case definition adequate?	a*	yes, with independent validation
		b	yes, eg. record linkage or based on self-report
		c	no description
2	Representativeness of the cases	a*	consecutive or obviously representative series of cases
		b	potential for selection biases or not stated
3	Selection of Controls	a*	community controls
		b	hospital controls
		c	no description
4	Definition of Controls	a*	no history of disease (endpoint)
		b	no description of source
5	Comparability of cases and controls on the basis of the design or analysis	a*	study controls for at least one variable (including age, sex and comorbidities)
		b**	study controls for more than one variable (including age, sex and comorbidities)
6	Ascertainment of exposure	a*	secure record (eg surgical records)
		b	structured interview blind to case/control status
		c	interview not blinded to case/control status
		d	written self-report or medical record only
		e	no description
7	Same method of ascertainment for cases and controls	a*	yes
		b	no
		c	unclear
8	Non-Response rate	a	same rate for both groups
		b	non respondents described
		c	rate different and no designation
For cohort studies, the quality criteria assessed are			
1	Representativeness of the exposed cohort	a*	truly representative
		b*	somewhat representative
		c	selected group of users
		d	no description
2	Selection of the non-exposed cohort	a*	drawn from the same community as the exposed cohort
		b	drawn from a different source
		c	no description of the derivation of the non-exposed cohort
3	Ascertainment of exposure	a*	secure record (eg surgical records)
		a*	structured interview
		c	written self-report
		d	no description
4	Demonstration that outcome of interest was not present at start of study	a*	yes
		b	no
		c	unclear
5	Comparability of cohorts on the basis of the design or analysis	a*	study controls for age or comorbidities
		b**	study controls for age and comorbidities
6	Assessment of outcome:	a*	independent blind assessment
		b*	record linkage
		c	self-report
		d	no description

7	Follow-up long enough for outcomes to occur	a*	yes
		b	no
		c	unclear
8	Adequacy of follow up of cohorts	a*	complete follow up – all that matters subjects accounted for, subjects lost to follow up unlikely to introduce bias - small number
		b*	inadequate numbers but description provided of those lost
		c	inadequate follow up rate and no description of those lost
		d	no statement

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

EW Only

Supplementary table S3: Study characteristics overview

Subgroup	All Studies	Bloodstream infections	Noninvasive infections
	87	57	10
Country			
South Korea ^{13,14,16,17,31,35,38,42,44,46,51,52,57,59}	14	9	2
Thailand ^{24,26,45,53-55,88}	7	3	
USA ^{10,18,28,32,48,61,69}	7	2	1
Spain ^{36,40,58,62,70,91,93}	7	4	2
Taiwan ^{12,39,64,71,82,84,96}	7	5	2
China ^{60,73,74,76,86}	5	4	
Israel ^{23,47,92,93}	4	3	
Germany ^{10,40,43,63}	4	3	
Italy ^{25,33,37}	3	3	
Japan ^{76,81,86}	3	3	
Tanzania ^{19,66,75}	3	3	
India ^{49,50,80}	3	1	1
Canada ^{65,67,85}	3	2	
UK ^{22,30,89}	3	3	
France ^{68,79}	2	1	1
South Africa ^{13,81}	2	1	
Brazil ^{21,34}	2	2	
Greece ⁹⁰	1	1	
Hungary ⁹⁵	1	1	
Lebanon ²⁷	1	-	
Malaysia ²⁹	1	-	1
Mexico ⁷²	1	1	
Saudi Arabia ²⁰	1	1	
Turkey ⁷⁸	1	1	
Continent			
Asia ^{12-14,16,17,20,23,24,25,27,29,31,35,38,39,42,44-47,49, 55,57,59,60,64,71,73,74,76,80-82,84,86-88,92,93,96}	46	29	6
Europe ^{11,22,25,30,33,35,37,40,41,43,58,62,63,68,70,78,79,89-91,94,95}	22	17	3
North America ^{10,18,28,32,48,61,65,67,69,85}	10	4	1
Africa ^{15,19,66,75,83}	5	4	-
South America ^{21,34,72}	3	3	-
More than 1 continent ⁵⁶	1	-	-

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Income group			
High-income countries ^{10-14,16-18,20,22,23,25,28,30-33,35-44,46-48,51,52,57-59,61-65,67-71,76,79,81,82,84-86,89-96,}	60	41	8
Low- and middle-income countries ^{15,19,21,23,25,27,29,34,45,50,53-55,60,66,72-75,77,78,80,83,87,88}	26	16	2
High-income countries AND Low- and middle-income countries ⁵⁶	1	-	-
Study design			
Case cohort study ^{10,12,24-28,31,40,44,46,55,58,61,63-65,67-69,85-87}	24	14	
Retrospective cohort study ^{11,13-17,20,21,23,29,33-38,41-43,45,47,48,50-54,59,60,71,73,74,76-78,81-84,88,89,93,95,96}	44	32	
Prospective cohort study ^{18,19,30,32,39,49,56,62,66,70,72,75,79,80,90-92,94}	18	11	
Year group			
1991-1999 ^{10,60,15,16,17,62,21,25,28,36,46,93,94}	13	10	-
2000-2009 ^{11-14,18-20,22-24,26,27,29-35,37-45,47,49-52,54,55,57,58,61,63,64,67-69,89-92,95,96}	49	31	6
2010-2018 ^{48,53,54,59,65,66,70-88}	25	16	4
Pathogen			
<i>Escherichia coli</i> ^{11,24,30,33,35-37,40,43,45,52,55,58,59,68,70,71,73,76,86,87,91,94}	23	16	3
<i>Klebsiella pneumoniae</i> ^{15,16,20,21,25,29,32,34,41,43,47,61,62,74,78,83,95,96}	17	11	1
<i>E. coli</i> and <i>K. pneumoniae</i> ^{10,13,14,17,26,28,38,43,44,46,48,50,51,54,57,60,63,69,85,88,89}	20	13	2
Gram-negative bacteria ^{12,18,19,22,23,27,31,39,42,49,53,56,64-67,72,75,77,79-82,84,90,92,93}	27	17	4
Study setting			
Entire hospital ^{10,11,16,18,20-27,29,30,33-38,40-46,48-50,52-55,58-60,62,65-69,73,74,76,82,85,86,90-96}	57	40	7
Intensive care unit ^{32,61,64,75,79-81,88,89}	9	5	1
Pediatric ward ^{17,19,28,51,57,78,83,88}	8	7	-
Neonatal ward ^{15,61,64,71,75}	5	3	-
Neonatal intensive care unit ^{61,64,75}	3	2	-
Medical ward ^{13,39,70}	3	-	2
Not provided ^{31,47}	2	-	-
Emergency Department ^{12,84}	2	2	-
Surgical ward ^{32,56}	2	-	-
Burn unit ³²	1	-	-
Oncology ⁷²	1	1	-
Referral centre for hepatopancreaticobiliary diseases ⁷⁷	1	-	-
Hematological ¹⁴	1	1	-

Study population			
All kinds of patients ^{10-13,14,18,20-27,29,30,34,35,39-41,43-46,48-50,52-56,58,60,62,63,65-69,76,82,84-86,90,92-95}	55	36	7
Intensive care unit patients ^{32,79-81,87,89}	6	3	1
Children ^{17,19,28,51,57,78,83,88}	8	7	-
Neonates ^{15,61,64,71,75}	5	3	-
Cancer patients ^{33,51,59,72,91}	5	5	-
Immunocompromised patients ⁵¹	1	1	-
Diabetic patients ⁹⁶	1	1	-
Elderly patients ⁷⁰	1	-	1
Patients with chemotherapy/stem cell transplantation ^{14,91}	2	2	-
Patients after prostatitis biopsy ⁴²	1	-	1
Lungs transplantation patients ⁴⁷	1	-	-
Hematological patients ⁷³	1	1	-
All except cardiothoracic therapy, transplant surgery, burns ⁷⁴	1	1	
Patients with pyogenic liver abscess ⁷⁷	1	-	-
Data reported			
Treatment information ^{10,12-13,23-25,30-38,40,44-49,51,52,54-65,67,68,70-96}	74	50	6
Appropriateness of treatment ^{10,12-14,16,17,19-21,23-26,30-38,40,44-46,48,49,51,52,54-56,58-60,62-65,67,68,70,72-74,76,77,79,81,83-86,89-96}	62	45	5
Empirical therapy ^{14,16,17,24,25,33,35-38,40,44,51,52,56,58,59,63,76,81,83,94}	22	16	2
Treatment outcome ^{10,12-21,25,26,30-38,40,44-49,51,52,54-57,59-65,67,68,72-74,76,78-81,83-86,88-92,94-96}	64	45	3
Minimum inhibitory concentration results ^{10,11,13,14,16-19,22-25,27,28,32,33,35-41,43,44,47,50-52,54-59,62,63,66,68,69,76-78,80,81,83,85-87,89,94,95}	52	34	4
AmpC genotyping ^{10,11,17,32,41,46,50,56,57,65,66,70,86}	13	6	2

Supplementary table S4: Characteristics for each study

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Lautenbach E ¹⁰	1997-1998	USA	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality; LOS	Risk factors for infection with ESBL-producing pathogens, difference in clinical outcomes of infections: resistant vs. susceptible organisms	EC, KP
Kim SH ¹⁴	2007-2008	South Korea	Cohort study, Retrospective	Non-ESBL-infection	Patients who received either chemotherapy or stem cell transplantation; neutropenic fever	Hematological ward, Others	All-cause mortality (28 day)	Risk factors for acquisition of ESBL, appropriateness of empirical antimicrobial therapy, clinical outcomes in relation to ESBL production	EC, KP
Chayakulkeere M ⁵³	2015-2015	Thailand	Cohort study, Retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Prevalence & risk factors for infections with & antibiotic susceptibility patterns of & outcomes of patients infected with ESBL-producing-GNB	GNB
Pisarntharak A ⁵⁴	2003-2007	Thailand	Cohort study, Retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Predictors for mortality associated with community-onset BSI with ESBL-producing pathogens, initial empirical antimicrobial regimens, associated hospital resource utilisation, costs accrued after diagnosis of BSI	EC, KP
Pisarntharak A ⁵⁵	2003-2004	Thailand	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Mortality associated with community-onset infection due to ESBL-producing pathogens, associated hospital resource use, post-infection hospital cost	EC
Jean SS ⁵⁶	2010-2011	Portugal, Columbia, the Philippines, Taiwan, Thailand	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Surgical ward	Attributable mortality, LOS	Clinical impact on hospitalised patients with community-acquired complicated intra-abdominal infection: ESBL-producing- vs. non-ESBL-producing pathogens	GNB
Lee J ⁵⁷	1999-2005	South Korea	interventional studies	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality (28 day)	impact of a change in antibiotic policy on ESBL-prevalence	EC, KP
Briongos-Figuero A ⁵⁸	2009-2010	Spain	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Characteristics & associated risk factors for EBSL-enterobacteria-UTIs	EC
Ha YE ⁵⁹	2010-2012	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients with cancer	Entire hospital	All-cause mortality (28 day)	Clinical & molecular epidemiology of ESBL-EC bacteraemia, clinical impact of ESBLs on patient outcome	EC
Du B ⁶⁰	1997-1999	China	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors for nosocomial ESBL-EC- and ESBL-KP- bacteraemia & influence on patient outcome.	EC, KP

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Stone PW ⁶¹	2001	USA	Case cohort study	Non-ESBL-infection	Neonates at NICU	NICU	LOS	costs of interventions aimed at controlling the outbreak, attributable length of stay associated with infection and colonisation with ESBL-KP	KP
Pillay T ¹⁵	1995-1996	South Africa	Cohort study, retrospective	Non-ESBL-infection	Neonates	Neonatal ward	All-cause mortality	Use of piperacillin/tazobactam in treatment of KP- infection	KP
Kim BN ¹⁶	1999-2000	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, LOS	Prevalence & clinical characteristics of ESBL-KP- bacteraemia, impact of ESBL- production on outcome of patients with KP- bacteraemia in endemic situation.	KP
Kim YK ¹⁷	1993-1998	South Korea	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality	Risk factors & clinical outcomes & clinical responses to treatment of ESBL-EC- and ESBL-KP-bacteraemia, prevalence and types of their ESBLs	EC, KP
Bhavnani SM ¹⁸	2001-2002	USA	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Risk factors for occurrence of invasive ESBL-EC- and ESBL-KP-infections, factors associated with clinical outcome, drug regimens for treatment of infections associated ESBL/non-ESBL strains in real-life clinical practice, clinical response rates for patients treated with cephalosporins/other classes of antimicrobial agents, /carbapenems, clinical response for those patients with infection associated with ESBL and non-ESBL-producing strains with MIC values V8 Ag/mL treated with cephalosporins.	GNB
Blomberg B ¹⁹	2001-2002	Tanzania	Cohort study, prospective	Non-ESBL-infection	Neonates, children	Pediatric ward	All-cause mortality	Prevalence & clinical implications of ESBL production in EC-,KP-, Salmonellae- septicemia	GNB
Pená C ⁶²	1993-1995	Spain	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Clinical epidemiology& outcome of ESBL-KP- bacteraemia, relevance of ESBL strains in mortality of patients with hospital-acquired KP-BSI.	KP
Kola A ⁶³	2002-2004	Germany	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS, ICU-LOS	Outcomes of ESBL-EC- and ESBL-KP-infections	EC, KP
Isai MH ⁶⁴	2001-2012	Taiwan	Case cohort study	Control group: non-ESBL-infection, second control group: all hospitalised patients	Neonates at NICU	NICU	Attributable mortality, all-cause mortality, LOS	Clinical features& risk factors& molecular epidemiology of ESBL-GNB	GNB
Maslikowska JA ⁶⁵	2010-2013	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS	Differences in clinical & microbiological outcome, mortality, and/or hospital resource use: ESBL-EC- and ESBL-Ks- vs non-ESBL-EC- and non-ESBL-Ks-infections	GNB

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Onken A ⁶⁶	2012-2013	Tanzania	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Most common bacterial pathogens causing BSI, antimicrobial susceptibility	GNB
Nguyen ML ⁶⁷	2005-2010	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS, ICU-LOS	Risk factors for & patient outcomes associated with ESBL-EC- and ESBL-Ks- bacteraemia, appropriateness of empiric antibiotic therapy & effect of inappropriate empiric therapy on outcomes	GNB
Denis B ⁶⁸	2005-2009	France	Case-control study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day), LOS	Prevalence & risk factors for ESBL-EC bacteraemia, impact on length of stay & 30day mortality	EC
Chopra T ⁶⁹	2004-2009	USA	Case cohort study	Case 2(Control1): non-ESBL-infection, second control group: no infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Predictors of ESBL-EC- and ESBL-KP-BSI, focus on cefepime exposure.	EC, KP
Panhotra BR ²⁰	2001-2003	Kingdom of Saudi Arabia	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors & clinical outcome of ESBL-KP-bacteraemia (hospital acquired)	KP
Marra AR ²¹	1996-2001	Brazil	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	ESBL-KP- associated mortality	KP
Skippen I ²²	2003-2005	UK	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors for & outcomes of ESBL-EC- and ESBL-KP-invasive transmission of organism in the healthcare setting	GNB
Schwaber MJ ²³	2000-2003	Israel	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Outcomes of ESBL-production in Enterobacteriaceae-bacteraemia.	GNB
Apisarnthanarak A ²⁴	2003-2004	Thailand	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	All adult patients	Entire hospital	All-cause mortality, LOS	Clinical & molecular epidemiologic factors associated with community onset ESBL-EC- infections, hospital resource utilisation, estimate costs associated with medical care (hospitalised patients)	EC
Umbarello M ²⁵	1999-2003	Italy	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS, ICU-LOS	Factors associated with isolation of ESBL- KP-strains	KP
Teistner R ¹¹	2008-2010	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital,	All-cause mortality, LOS	Difference in mortality: ESBL-EC-BSIs vs. non-ESBL-EC-BSIs, molecular epidemiology of ESBL-positive isolates	EC

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Apisarntharak A ²⁶	2003-2004	Thailand	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Risk factors for & outcomes of ESBL-EC- and ESBL-KP-infections (healthcare associated)	EC, KP
Kanafani ZA ²⁷	2003	Lebanon	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Epidemiology of infections with ESBL-EC and ESBL-Ks at AUBMC risk factors & outcomes of infections - focus on effect of prior antibiotic administration & the risks imparted by specific classes of antimicrobial agents	GNB
Zaoutis TE ²⁸	1999-2003	USA	Case cohort study	Non-ESBL-infection	Children	Entire hospital	All-cause mortality, LOS	Risk factors & outcomes associated with ESBL-EC-and ESBL-KP-BSI	EC, KP
Goh LC ²⁹	2003-2004	Malaysia	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Impact of ESBL-KP-respiratory tract infections on hospital mortality, requirement for mechanical ventilation & length stay	KP
Melzer M ³⁰	2003-2005	UK	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Differences in mortality & length of hospital stay & time from bacteraemia to death in patients with ESBL-EC- vs. non-ESBL-EC-bacteremic-infection	EC
Song KH ³¹	2000-2006	South Korea	Case cohort study	Non-ESBL-infection	Patients with spontaneous bacterial peritonitis	Not provided	All-cause mortality (28 day)	Outcomes of ESBL-EC-and ESBL-Ks- vs non-ESBL-EC-and ESBL-Ks-SBP (based on isolation from ascites), impact of ineffective initial antimicrobial therapy on outcome in patients with ESBL-EC- and ESBL-Ks-SBP, risk factors for infection by ESBL-producing microorganisms.	GNB
Bennett JW ³²	2004-2008	USA	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU, Surgical ward, Burn unit	All-cause mortality (28 day)	ESBL types and strain variability, presence of host factors to determine potential role in morbidity and mortality during ESBL-KP-infections	KP
Recarichi EM ³³	2000-2007	Italy	Cohort study, retrospective	Non-ESBL-infection	Patients with hematological malignancies	Entire hospital	All-cause mortality (28 day)	Risk factors for mortality in patients suffering from hematological malignancies with concurrent EC-bacteraemia. Focus on impact of ESBL- production & fluoroquinolone resistance by bacterial isolates	EC
Fuon FF ³⁴	2006-2009	Brazil	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day), LOS	Risk factors & mortality rate in ESBL-KP-bacteraemia	KP
Kang CI ³⁵	2008-2009	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Risk factors of ESBL-EC among community-onset bacteraemia, treatment outcomes	EC

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Pena C ³⁶	1996-2003	Spain	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Risk factors for mortality among patients with EC- infections	EC
Tumbarello M ³⁷	2006	Italy	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	ICU, Medical ward, Entire hospital, surgical wide	All-cause mortality (21 day), LOS	Clinical & economic impacts of ESBL production, inadequate Initial Antibiotic Therapy of EC-BSI	EC
Kang C ³⁸	2006-2009	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality (28 day)	Impact of ESBL-producing bacteraemia on outcome in patients with hematologic malignancy.	EC, KP
Wu YH ³⁹	2009-2012	Taiwan	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Medical ward	LOS	Host-related risk factors for community-onset UTI due to levofloxacin- or cefazolin-nonsusceptible isolates or uropathogens with ESBL production, clinical impact of UTIs due to antimicrobial-nonsusceptible pathogens	GNB
Rodriguez-Bano J ⁴⁰	2004-2006	Spain	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Epidemiology & risk factors (focus on previous antimicrobial use) & mortality rate for patients with ESBL-EC-COBSI	EC
Gürttnke S ⁴¹	2008-2011	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Distribution of ESBL genotypes, hospital mortality in cases of ESBL-KP-BSI	KP
Oh MM ⁴²	2006-2011	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients after Prostatitis Biopsy	Entire hospital	LOS	Impact of ESBL-positive-strains on clinical course & progression to chronic prostatitis in patients with postbiopsy acute prostatitis.	GNB
Leistner R ⁴³	2008-2011	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Financial disease burden attributable to ESBL-positive species in cases of EC-and KP-BSI	EC, KP
Lin JN ⁴²	2005-2009	Taiwan	Case cohort study	Non-ESBL-infection	All kinds of patients	Emergency Room	Attributable mortality, all-cause mortality (28 day), LOS, ICU-LOS	Clinical & microbiological characteristics, risk factors for acquisition of infection, prescription of initial empirical antibiotics mortality rate of infection	GNB
Ku NS ⁴⁴	2006-2010	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Clinical usefulness of breakpoints for treatment of Enterobacteriaceae-bacteraemia, (focus on EC- and Ks-bacteraemia): CLSI 2009- vs. CLSI 2010-guidelines.	EC, KP

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Anunnatsiri S ⁴⁵	2005-2006	Thailand	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Incidence of ESBL-EC-septicemia, factors associated with infection & clinical outcomes	EC
Kang CI ⁴⁶	1998-2002	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Hospital-wide	All-cause mortality (28 day)	Risk factors for mortality & treatment outcome of ESBL-EC- and ESBL-KP-BSI	EC, KP
Raviv Y ⁴⁷	2004-2007	Israel	Cohort study, retrospective	Control group: non-ESBL-infection, second control group: no infection	patients with lung transplantation	Not provided	All-cause mortality (28 day)	Outcomes of lung transplant recipients infected by CRKP and ESBL carbapenem-sensitive KP (referred to MDR-KP)	KP
Kim HJ ¹³	2005-2010	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Medical ward	All-cause mortality (28 day), LOS	Clinical outcome of patients with biliary tract infection: ESBL-producing bacterial isolates vs. non-ESBL-producing-bacterial isolates, predictors of poor prognosis, impact of ineffective antimicrobial therapy on clinical outcome	EC, KP
MacVane SH ⁴⁸	2011-2012	USA	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS	clinical & economic outcomes of patients with ESBL-EC- and ESBL-KP-UTI vs. non-ESBL-EC- and non-ESBL-KP-UTI	EC, KP
Abhilash KP ⁴⁹	2007	India	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Prevalence & risk factors & outcome of antibiotic treatment among hospitalised patients with ESBL-EC- and ESBL-Ks-BSI	GNB
Rhantni M ⁵⁰	2006	India	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Prevalence & impact on clinical outcome of ESBL-production among nosocomial isolates of EC & KP	EC, KP
Han SB ⁵¹	2009-2013	South Korea	Cohort study, retrospective	Non-ESBL-infection	Children (immunocompromised, with cancer, neutropenic fever)	Pediatric ward	Attributable mortality, all-cause mortality (28 day)	Clinical outcomes of ESBL-EC- and ESBL-KP-bacteraemia & their antibiotic susceptibilities	EC, KP
Lee S ⁵²	2009-2011	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients with Acute Pyelonephritis	Entire hospital	All-cause mortality (14 day), LOS	Impact of ESBL on clinical outcomes of Acute Pyelonephritis treated with empirical ceftriaxone (which was inappropriate for ESBL-producing organisms)	EC
Artero A ⁷⁰	2013-2015	Spain	Cohort study, prospective	Non-ESBL-infection	Elderly	Medical ward	All-cause mortality, LOS	Identify clinical factors to predict ESBL-EC among elderly patients with UTI admitted to hospital in a high rate setting of ESBL-EC	EC

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Chen IL ⁷¹	2004-2015	Taiwan	Cohort study, retrospective	Non-ESBL-infection	Neonates	Neonatal ward	All-cause mortality	Compare the clinical characteristics & laboratory data of preterm babies with EC BSI: survival vs. nonsurvival groups, ESBL vs non-ESBL groups, determine the predictive factors of EC BSI in preterm babies	EC
Islas-Munoz B ⁷²	2016-2017	Mexico	Cohort study, prospective	Non-ESBL-infection	Cancer patients	Oncological ward	All-cause mortality (28 day)	Evaluate the clinical epidemiological characteristics & risk factors associated with mortality in cancer patients with BSI-special emphasis on MDR bacteria	GNB (and others)
Ma J ⁷³	2012-2015		Cohort study, retrospective	Non-ESBL-infection	Patients with hematological diseases	Entire hospital	All-cause mortality (28 day)	Evaluate the antimicrobial resistance & clinical features & risk factors for septic shock & death of nosocomial EC-BSI	EC
Man MY ⁷⁴	2009-2016	China	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients, except patients from Burn unit, transplant surgery ward or with thoracic therapy	Entire hospital	All-cause mortality (28 day)	Evaluate the incidence & clinical characteristics & outcomes of patients with KP BSI in critical care & general ward settings	KP
Marando R ⁷⁵	2016	Tanzania	Cohort study, prospective	Non-ESBL-infection	Neonates	NICU	All-cause mortality	Investigate factors associated with ESBL-PE neonatal sepsis & mortality among neonates, characterise selected isolates to show virulence potential & transmission dynamics	GNB
Namikawa H ⁷⁶	2011-2015	Japan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Investigate clinical characteristics of patients with ESBL-EC-BSI	EC
Shi SH ⁷⁷	2008-2015	China	Cohort study, retrospective	Non-ESBL-infection	Patients with pyogenic liver abscess	Centre for hepatopancreaticobiliary diseases	All-cause mortality, LOS	Aetiology & morbidity & clinical characteristics of pyogenic liver abscess caused by ESBL-PE	GN
Tanir Basaranoglu S ⁷⁸	2011-2015	Turkey	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality (28 day)	Assess risk factors for health care associated ESBL-KP-BSI in children, analyze clinical outcomes: ESBL-KP vs. non-ESBL-KP	KP
Bazazi K ⁷⁹	2009-2015	France	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality, LOS, ICU-LOS	Determine, among ESBL-PE carriers, the prevalence & associated factors & clinical impact of ESBL-PE pneumonia, determine factors associated with ICUAP caused by carbapenem-resistant bacteria	GNB

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Ray S ⁸⁰	2014-2016	India	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Investigate spectrum of microbial resistance pattern in the community and their effects on mortality	GNB
Haruki Y ⁸¹	2006-2016	Japan	Cohort study, retrospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Compare the clinical characteristics & outcomes of critically ill patients in an ICU, who were hospitalised for BSI caused by ESBL-EC or non-ESBL-EC.	GNB
Lin WT ⁸²	2009-2014	Taiwan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Investigate the clinical manifestations & bacteriological features of culture-proven, GNB arthritis	GNB
Guys H ⁸³	2006-2011	South Africa	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality	Describe the clinical presentation of KPBSI, risk factors associated with ESBL-KPBSI, antibiotic susceptibility patterns of the KP isolates & KPBSI mortality including factors associated with in-patient mortality	KP
Lee CC ⁸⁴	2008-2013	Taiwan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Emergency Department	Attributable mortality, all-cause mortality (28 day), LOS, ICU-LOS	Analyse the impact of ESBL-producing isolates on the outcome of bacteremic patient after controlling for baseline patient characteristics & bacteraemia severity by using a propensity-matched analysis (PSM)	GNB
Huang YY ⁸⁵	2011-2013	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Determine cumulative incidence of ESBL urosepsis, identify major risk factors for ESBL urosepsis, determine impact of international travel on development of ESBL urosepsis	EC, KP
Komatsu Y ⁸⁶	2008-2013	Japan	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Identify risk factors & clinical outcomes in patients with BSI due to ESBL- or carbapenemase-producing EC, determine prevalence & genetic background	EC
Liu MM ⁸⁷	2011-2016	China	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	ICU-patients	ICU	All-cause mortality	Identify risk factors for ESBL-producing ECBSI among carriers at ICU	EC
Nivesvivat T ⁸⁸	2010-2017	Thailand	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality, LOS	Determine prevalence, risk factors & clinical outcomes of ESBL-producing EB in paediatric BSI	EC, KP

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Cordery RJ ⁸⁹	2004-2006	UK	Cohort study, retrospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Elucidate specific risk factors for the acquisition of ESBL infection in the ICU; all-cause mortality (in ICU) compared in patients with infections due to ESBL- and non-ESBL-producing organisms	GNB
Paikos GL ⁹⁰	2003-2005	Greece	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Identify risk factors associated BSI caused by integron-carrying EB; evaluate the consequences of these genetic elements on patient outcome	GNB
Gudiol C ⁹¹	2006-2008	Spain	Cohort study, prospective	Non-ESBL-infection	Cancer patients and hematopoietic stem cell transplant patients	Entire hospital	All-cause mortality	Assess clinical features, risk factors, molecular epidemiology & outcome of ESBLEC BSI in hospitalised cancer patients	EC
Marchaim D ⁹²	2006-2008	Israel	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Define predictors & outcomes of ESBL BSI among patients with bacteraemia due to EB upon hospital admission	GNB
Menashe G ⁹³	1997	Israel	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Determine: prevalence of ESBL-P organisms among adult patients with nosocomial EB BSI treated in our institution; association between ESBL production & resistance to other antibiotics; clinical characteristics of patients with nosocomial ESBL-P BSI compared with those infected with non-producing strains; impact of ESBL production on outcome of patients with nosocomial EB BSI	GNB
Ortega M ⁹⁴	1991-2007	Spain	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Describe source, resistance rate to fluoroquinolone & beta-lactam antibiotics and mortality of EC BSI episodes in a single institution; identify predictive factors for isolation of fluoroquinolone-resistant or ESBL- producing strains.	EC
Sziglyi M ⁹⁵	2005-2008	Hungary	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality,	Investigate risk factors for & outcomes of BSI caused by ESBL-producing and ESBL-non-producing KP	KP
Tsai SS ⁹⁶	2005-2006	Taiwan	Cohort study, retrospective	Non-ESBL-infection	Diabetic patients	Entire hospital	All-cause mortality	Analyze characteristics, risk factors & outcomes of diabetic patients with community- vs. hospital-acquired KP BSI	KP

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3 EC = *Escherichia coli*
4 KP = *Klebsiella pneumoniae*
5 GNB = Gram-negative bacteria
6 BSI = Bloodstream infection
7 UTI = Urinary tract infection
8 ICU = Intensive care unit
9 NICU = Neonatal intensive care unit
10 ESBL-PE = Extended-spectrum beta-lactamase-producing Enterobacteriaceae
11 EB = Enterobacteriaceae
12 LOS = Length of stay
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Supplementary table S5: Risk of bias assessment of case cohort studies according to Newcastle - Ottawa quality assessment scale:

Assessment criteria / Study author	1. Is the case definition adequate?	2. Representativeness of the cases:	3. Selection of Controls	4. Definition of Controls	5. Comparability of cases and controls on the basis of the design or analysis	6. Ascertainment of exposure	7. Same method of ascertainment for cases and controls	8. Non-Response rate
Lautenbach, E.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Apisarntharak, A.	Green	Green	Yellow	Green	Green	Green	Green	Green
Briongos-Figuero, L-S.	Green	Green	Yellow	Yellow	Grey	Green	Green	Green
Stone, P.W.	Green	Green	Brown	Yellow	Grey	Green	Green	Green
Kola, A.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Tsai, M.H.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Maslikowska, J.A.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Nguyen, M. L.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Denis, B.	Green	Green	Yellow	Green	Yellow	Green	Green	Green
Chopra, T.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Skippen, I.	Green	Green	Yellow	Yellow	Yellow	Green	Grey	Green
Apisarntharak, A.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Tumbarello, M.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Apisarntharak, A.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Kanafani, Z. A.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Zaoutis, T. E.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Song, K. H.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Kang, C. I.	Green	Green	Yellow	Yellow	Grey	Green	Green	Green
Rodriguez-Bano, J.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Lin, J. N.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Ku, N. S.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Kang, C. I.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Huang, Y. Y.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Komatsu, Y.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Liu, M. M.	Green	Green	Yellow	Green	Yellow	Green	Green	Green

Risk of bias assessment of cohort studies according to Newcastle - Ottawa quality assessment scale:

Study author / Assessment criteria	1. Representativeness of exposed cohort	2. Selection of non-exposed cohort	3. Ascertainment of exposure	4. Demonstration that outcome of interest not present at start	5. Comparability based on design or analysis	6. Assessment of outcome	7. Follow-up long enough for outcome	8. Adequacy of follow up of cohorts
Jean, S.S.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
Bhavnani, S. M.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Blomberg, B.	Yellow	Green	Green	Green	Grey	Yellow	Green	Green
Pena, C.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Onken, A.	Green	Green	Green	Green	Grey	Yellow	Green	Green
Melzer, M.	Green	Green	Green	Green	Grey	Yellow	Green	Green
Bennet, J.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Wu, Y.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Abhilash, K.	Green	Green	Green	Green	Green	Yellow	Yellow	Green
Artero, A.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Islas-Munos, B.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Marando, R.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Razazi, K.	Green	Green	Green	Green	Green	Yellow	Green	Green
Ray, S.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Panhotra, B.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Kim, S.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Chayakulkeeree, M.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Apisarnthanarak, A.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Ha, Y.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Du, B	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Pillay, T.	Yellow	Green	Green	Green	Grey	Yellow	Green	Green
Kim, B.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Kim, Y	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Marra, A.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Schwaber, M.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Leistner, R.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Loh, L.C.	Green	Green	Green	Green	Green	Yellow	Green	Red
Trecarichi, E.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Tuon, F.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Kang, C. I.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Pena, C.	Green	Green	Green	Green	Grey	Yellow	Green	Green
Tumbarello, M.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Gurntke, S.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Oh, M.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Leistner, R.	Green	Green	Green	Green	Grey	Yellow	Green	Green
Anunnatsiri	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green

1	Raviv, Y.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
2	Kim, H.J.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
3	MacVane, S.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
4	Shanthi	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
5	Han, S.B.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
6	Lee, S.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
7	Chen, I-L.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
8	Ma, J.	Green	Green	Green	Green	Green	Yellow	Green	Green
9	Man, M.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
10	Namikawa, H.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
11	Shi, S.	Yellow	Green	Green	Green	Grey	Yellow	Green	Green
12	Tanir Basarangolu, S.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
13	Haruki, Y.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
14	Lin, W.	Green	Green	Green	Green	Grey	Yellow	Green	Green
15	Buys, H.	Green	Green	Green	Green	Green	Yellow	Green	Green
16	Lee, C.C.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
17	Nivesvivat, T.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
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Supplementary table S6: Source of heterogeneity among effect estimates in studies on ESBL bloodstream infections in comparison with patients with non-ESBL bloodstream infections assessed using univariate meta-regression:

Subgroups / Outcome	All-cause mortality	Length of Stay
Mortality time	0.85	-
Pathogen	0.45	0.34
Study design	0.51	0.21
Study country	0.22	0.09
Income classification	0.17	0.80
Study period	0.57	0.78
Study setting: ICU ward	0.78	0.97
Study setting: Neonatal ward	0.62	0.97
Study setting: Pediatric ward	0.96	0.96
Study population: ICU patients	1.00	-
Study population: Children	0.96	0.96
Study population: Neonates	0.62	0.97
Information about therapy	0.53	
Appropriateness of therapy reported	0.68	
Information about outcome of therapy	0.74	-
MIC reported	0.28	-



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	5,6



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	suppl.material
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8 and suppl. material
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	suppl.material
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8 and suppl. material
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7,8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11



PRISMA 2009 Checklist

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BMJ Open

Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria producing extended-spectrum beta-lactamases: a systematic review and meta-analysis

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3 1 **Variation of effect estimates in the analysis of mortality and length of hospital stay in**
4 **patients with infections caused by bacteria producing extended-spectrum beta-**
5 **lactamases: a systematic review and meta-analysis**
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1 **ABSTRACT**

2 **Objective** To assess the variation of effect estimates in the analysis of mortality and length of
3 stay (LOS) in patients with infections caused by extended-spectrum beta-lactamase (ESBL)-
4 producing *Enterobacteriaceae*.

5 **Design** Systematic review and meta-analysis

6 **Methods** Literature search for clinical studies from 1 January 1960 to 1 October 2018 was
7 conducted in PubMed. Primary outcomes were risk ratios (RRs) of all-cause and attributable
8 mortality and weighted mean differences (WMDs) in LOS in patients with bloodstream
9 infections (BSIs) and non-invasive infections. Any change in the effect estimates was
10 assessed by grouping studies according to design, setting, economy-based country
11 classification, reporting period, microbiological aetiology, infection type, and adjustment for
12 appropriateness of empirical treatment. The impact of ESBL production was calculated using
13 random effect meta-analysis and heterogeneity was evaluated by I^2 statistics and
14 metaregression.

15 **Results** Eighty-four studies including 22,030 patients and 149 outcome measures were
16 included in the meta-analysis. Most studies were retrospective cohorts from high-income
17 countries, providing unadjusted estimates. ESBL production in patients with BSIs (56 studies)
18 increased the RR for all-cause mortality by a factor of 1.70 (95% CI: 1.52-1.90; $p < 0.001$),
19 attributable mortality (16 studies) by 1.75 (95% CI: 1.448-2.108; $p < 0.001$), and WMD in the
20 intensive care unit by 3.07 days (95% CI: 1.61-4.54; $p < 0.001$). WMD in hospital LOS was
21 significantly higher in BSIs (4.41 days; 95% CI: 3.37-5.46; $p < 0.001$) and non-invasive (2.19
22 days; 95% CI: 1.56-2.81; $p < 0.001$). Subgroup analyses showed variation of estimates by
23 study design, population, strain, and assessment of appropriateness of empiric treatment. High
24 heterogeneity was observed in all analyses.

25 **Conclusions** Current evidence of the clinical burden of infections caused by ESBL-producing
26 bacteria is highly heterogeneous and based mainly on unadjusted estimates derived from
27 retrospective studies. Despite these limitations, ESBL production in strains causing BSIs
28 seems associated with higher all-cause and attributable mortality and longer hospitalisation.

29 **KEYWORDS**

30 Extended-spectrum beta-lactamase, mortality, bloodstream infection, length of stay, meta-
31 analysis, systematic review
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1 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

- 2 ▶ Evidence of the impact of ESBL production on mortality and length of stay in strains
- 3 causing bacteremic and non-bacteremic infections was collected systematically.
- 4 ▶ Effect of multiple epidemiological and clinical variables was assessed in the calculation of
- 5 estimates.
- 6 ▶ Heterogeneity among studies was assessed.
- 7 ▶ Only few studies had been performed in high-risk populations or low-income countries.

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1 INTRODUCTION

2 Infections caused by extended-spectrum beta-lactamase (ESBL)-producing
3 *Enterobacteriaceae* are responsible for high morbidity and mortality worldwide.^{1,2,3} The 2018
4 World Health Organization list of antibiotic-resistant pathogens identified mortality as the
5 most important criteria to prioritise bacteria for research and development of new, effective
6 antibiotics.¹ In this prioritisation exercise, ESBL-producing *Enterobacteriaceae* were
7 designated a critical priority because of their high all-cause mortality and high prevalence
8 globally in healthcare-associated and community-acquired infections. The incidence and
9 attributable mortality of multidrug-resistant bacterial infections, including ESBL-producing
10 *Enterobacteriaceae*, in European countries has been recently estimated using a modelling
11 analysis.⁴ In 2015 ESBL-producing *Escherichia coli* was responsible for almost 300,000
12 infections in Europe and 9,000 attributable deaths, and ESBL-producing *Klebsiella*
13 *pneumoniae* caused around 70,000 infections and more than 3,500 deaths. The major
14 limitation of this analysis is the sparseness of evidence on mortality due to ESBL-producing
15 bacteria, which was limited largely to studies conducted in high-income countries.

16 Two systematic reviews have been performed to define the impact of ESBL production on
17 mortality due to *Enterobacteriaceae*.^{2,3} Both meta-analyses included studies targeting
18 bloodstream infections (BSIs) and showed doubling all-cause mortality for ESBL-associated
19 bacteraemia compared to non-ESBL *Enterobacteriaceae* bacteraemia. A major drawback of
20 the analyses, highlighted by the authors, was the lack of control for confounding and limited
21 adjustment for empiric therapy. No systematic review has been performed to assess
22 attributable mortality and other indicators of clinical impact such as length of stay (LOS).

23 Because estimates of clinical burden drive policy design for antibiotic stewardship and
24 infection control interventions, precise and current estimates are essential. The objective of
25 this systematic review and meta-analysis was to assess the variation of effect estimates in the
26 analysis of mortality and LOS in patients with infections due to ESBL-producing
27 *Enterobacteriaceae*.

28 METHODS

29 Literature search strategy

30 The search was performed by 2 researchers (BPG and PS) in PubMed on 05 October 2018
31 using search terms (supplementary table S1) relevant to the following combinations: (ESBL
32 AND *Escherichia coli* AND mortality) OR (ESBL AND *Klebsiella pneumoniae* AND
33

1 mortality) OR (ESBL AND Escherichia coli AND length of stay OR length of hospitalisation)
2 OR (ESBL AND Klebsiella pneumoniae AND length of stay OR length of hospitalisation).
3 Reference lists of retrieved articles were also searched.

4 **Eligibility criteria**

5 We included all clinical studies with a comparison group assessing all-cause mortality,
6 attributable mortality, and overall LOS and intensive care unit stay (ICU) LOS in hospitalised
7 patients with ESBL infections. Studies published from 1 January 1960 to 1 October 2018
8 irrespective of the clinical setting and study design were included. No language restriction has
9 been applied. Diagnostic studies, reviews, case reports, non-clinical studies, and abstracts of
10 conference presentations were not included.

11 **Data extraction**

12 Two reviewers (PS and BPG) independently assessed the eligibility of trials and extracted
13 data. In case of disagreement, a third reviewer (DL) was consulted. Extracted data were
14 collected in an electronic worksheet, using EpiInfo 7.1: authors, journal, country, year of
15 publication, year of study, time of data collection, study design, comparison group, study
16 setting, population, aetiology, type and site of infection, and raw data related to mortality and
17 LOS/ICU-LOS. Countries were classified as high-, middle-, or low-income using the World
18 Bank Atlas method.⁵ Adjusted effect estimates such as odds ratios (ORs) or hazard ratios and
19 quality indicators such as reporting of antibiotic therapy, appropriateness of empirical
20 treatment, resistance mechanisms, and minimum inhibitory concentrations (MICs) were also
21 extracted.

22 Mortality data were extracted as all-cause mortality or attributable mortality as defined in the
23 studies. Where available, prespecified time periods for mortality assessment (i.e., 14 days, 28
24 days, in-hospital) were also extracted. LOS and ICU-LOS were extracted as days with mean
25 and standard deviation or median and interquartile range.

26 **Data analysis**

27 The primary outcomes for the clinical impact of ESBL infections were RRs of all-cause and
28 attributable mortality and the weighted mean difference (WMD) in LOS and ICU-LOS in
29 patients with ESBL infections compared with those in patients with non-ESBL infections and,
30 where available, with uninfected patients. The impact of ESBL production on attributable and
31 all-cause mortality was calculated with random effect meta-analysis and expressed as RR with

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3 1 95% confidence interval (CI). WMD in days with 95% CI was calculated to express the
4 2 excess in LOS and ICU-LOS.

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7 3 Variation of the effect estimate was assessed by grouping the studies according to the
8 4 following study/outcome characteristics: mortality time assessment (7 vs 14 days), aetiology
9 5 (*E. coli* vs *K. pneumoniae*), infection localisation, clinical setting (paediatric, oncology, ICU),
10 6 economic country areas (high-income countries [HICs] vs low- and medium-income countries
11 7 [LMICs]), study design, assessment of empiric therapy, and year. Studies were classified
12 8 according to the type of infections evaluated. Studies on BSIs were defined as those in which
13 9 patients had positive blood cultures and were admitted to the hospitals with signs and
14 10 symptoms of systemic inflammatory response and requiring therapy, similarly to the
15 11 definition adopted by the most recent cohort studies on ESBL infections.⁶ Non-invasive
16 12 infections included non-bacteremic patients with only localised signs and symptoms of
17 13 infection (such as urinary tract infections or superficial surgical site infections).

18
19 14 Subgroup analysis was computed only if more than 2 studies were available for each group.
20 15 Heterogeneity was evaluated by using I^2 statistics and metaregression. Overall significance
21 16 testing was carried out using Wald tests adjusted using the Bonferroni correction. The
22 17 unadjusted ORs were compared with the adjusted ORs to estimate the effect of adjustment.
23 18 Reporting and publication bias was presented in funnel plots (supplementary figure 1 and 2)
24 19 and tested by Egger's test. Statistical analyses were performed using Stata version 15. Risk of
25 20 bias was assessed independently by two authors (PS, DL) using the Newcastle - Ottawa
26 21 quality assessment scale for cohort studies.⁷ Studies were classified as low, moderate, or
27 22 high quality according to AHRQ standards (supplementary table S2). All meta-analyses
28 23 were performed in accordance with the Cochrane Collaboration recommendations⁸ and
29 24 reported according to the PRISMA statement.⁹

30 25 The protocol is available online.
31 26 ([https://im1-tuebingen.de/wp-](https://im1-tuebingen.de/wp-content/uploads/2019/03/ClinicalImpactAMR_SR_studyprotocol_2018.pdf)
32 27 [content/uploads/2019/03/ClinicalImpactAMR_SR_studyprotocol_2018.pdf](https://im1-tuebingen.de/wp-content/uploads/2019/03/ClinicalImpactAMR_SR_studyprotocol_2018.pdf))

33 28 **Patient and Public Involvement**

34 29 There was no patient or public involvement in this systematic review of published literature.

35 30 **RESULTS**

36 31 Our literature search identified 1006 studies, and 92 (9.2%) met the eligibility criteria on the
37 32 basis of abstract screening. Full-text screening excluded an additional 5 articles, providing an

1 evidence base of 87 studies (Figure 1).¹⁰⁻⁹⁶ The 87 studies included in the qualitative analysis
2 were conducted between 1991 and 2017 in 25 countries, mainly in South Korea (14 studies),
3 Thailand (7), USA (7), Taiwan (7), and Spain (7). Sixty (68.9%) studies were performed in
4 HICs, 26 (29.9%) in LMICs, and 1 included both HICs and LMICs.⁵⁶ About half (44, 50.6%)
5 were retrospective cohort studies, 24 (27.6%) case cohort studies, and 18 (20.7%) prospective
6 cohort studies; 1 study had an interventional design.⁵⁷ The comparison group was patients
7 with infections caused by gram-negative non-ESBL producers in 82 (94.3%) studies, non-
8 infected patients in 2 (2.3%), and both control groups in 3 (3.5%). Most (57, 65.5%) studies
9 included data from the entire hospital, while a few focused on specific settings, mainly ICUs
10 (9, 10.3%) and paediatric wards (8, 9.2%). The most common ESBL-producing bacteria were
11 *E. coli* (23, 26.4%) and *K. pneumoniae* (17, 19.5%). An overview of study characteristics is
12 provided in online supplementary table S3.

13 Because data in 3 studies^{22,61,87} were insufficient for quantitative analysis, 84 (96.6%) studies
14 were included in the meta-analysis analysing data from 22,030 patients and 149 outcome
15 measures. Fifty-seven studies analysed BSIs and 10 non-invasive infections. Study
16 characteristics for all studies are provided in online supplementary table S4. 49 (58.3%)
17 studies were of high quality, 23 (27.3%) were of moderate quality, and 12 (14.3%) were of
18 low quality (supplementary table S5).

19 **All-cause mortality**

20 All-cause mortality was reported in 81 studies including 21,942 patients (56 on BSIs and 7 on
21 non-invasive infections). ESBL production in patients with BSIs increased all-cause mortality
22 by a factor of 1.70 (95% CI: 1.52-1.90; $p < 0.001$; $I^2 = 45.3%$; $p < 0.001$) while studies including
23 non-invasive reported a RR of 1.58 (95% CI: 1.23-2.02; $p < 0.001$) (supplementary figure 3).
24 Among the BSI patients, the RR increased over time from 1.56 (95% CI: 1.15-2.11; $p = 0.004$)
25 in 1991-1999 to 1.74 (95% CI: 1.50-2.01; $p < 0.001$) in 2000-2009, and it was stable in 2010-
26 2018 (1.72, 95% CI: 1.39-2.13; $p < 0.001$). The RR was higher in studies assessing
27 appropriateness of empiric therapy (RR=1.75; 95% CI 1.54-1.99; $p < 0.001$) than in those that
28 did not (RR=1.55; 95% CI 1.26-1.90; $p < 0.001$). The subgroup analysis by pathogen showed
29 that ESBL production increased the RR in BSIs due to *E. coli* (RR=1.82; 95% CI: 1.50-2.21;
30 $p < 0.001$) compared to those due to *K. pneumoniae* (RR=1.48; 95% CI: 1.17-1.87; $p = 0.001$).
31 Stratification by population age showed a higher RR in paediatric population (RR=2.09; 95%
32 CI: 1.62-2.71; $p < 0.001$). Effect estimates did not vary significantly by study country,
33 mortality time assessment (14 vs 28 days), ESBL molecular resistance mechanisms, or study

1 design (Figure 2 and online supplementary figure 4). Adjusted estimates for inappropriate
2 empirical antibiotic therapy were provided for 14 studies. The pooled unadjusted OR for all-
3 cause mortality was 2.91 (95% CI: 2.23-3.81; $p < 0.001$, $I^2 = 27.1\%$; $p = 0.164$) and the pooled
4 OR after adjusting for receipt of appropriate empirical treatment was 3.22 (95% CI: 1.53-
5 6.76; $p = 0.002$; $I^2 = 87.5\%$; $p < 0.001$). The impact of ESBL production on LOS and mortality
6 varied according to the infection type, with higher effect in intra-abdominal, respiratory and
7 BSIs (supplemental figure 5 and 6).

8 **Attributable mortality**

9 Attributable mortality was analysed in 16 studies including 2,885 patients. All studies were
10 performed in HICs. ESBL production in patients with BSIs increased the risk of attributable
11 mortality by a factor of 1.75 (95% CI: 1.45-2.11; $p < 0.001$; $I^2 = 0\%$; $p < 0.001$). The RR
12 increased over time from 1.53 (95% CI: 1.10-2.12; $p = 0.011$) in 1991-1999 to 1.91 (95% CI:
13 1.43-2.54; $p < 0.001$) in 2000-2009 (Figure 3). Pathogen-specific RR for attributable mortality
14 was 1.60 (95% CI: 1.18-2.15; $p = 0.002$) for *K. pneumoniae* and 1.76 (95% CI: 1.33-2.34;
15 $p < 0.001$) when the gram-negative organisms were analysed all together without species
16 differentiation. The subgroup analysis showed the RR was lower in case cohort studies (1.56;
17 95% CI: 1.09-2.25; $p = 0.016$) than in cohort studies (1.80; 95% CI: 1.37-2.37; $p < 0.001$).

18 **Length of stay**

19 LOS data were provided in 37 studies (17 on BSIs and 8 on non-invasive) analysing 38
20 outcome measures. The WMD of LOS in patients with BSIs was 4.41 days (95% CI: 3.37-
21 5.46; $p < 0.001$) and decreased from 5.72 days (95% CI: 2.69-8.75; $p < 0.001$) in 1991-1999 to
22 4.22 days (95% CI: 3.02-5.43; $p < 0.001$) in 2000-2009 and was stable up to 2018 (4.30 days;
23 95% CI: 1.38-7.22; $p = 0.004$). Higher WMD ($p < 0.001$) was observed for BSIs due to *K.*
24 *pneumoniae* (7.67 days; 4.63-10.71) than for those due to *E. coli* (6.07 days; 95% CI 3.71-
25 8.43). Retrospective cohort studies reported higher ($p < 0.001$) WMD (6.43 days; 95% CI:
26 4.66-8.21; $p < 0.001$) than case cohort studies (3.32 days; 95% CI: 2.03-4.61). Studies in HICs
27 showed higher WMD (4.56 days; 95% CI 3.43-5.70; $p < 0.001$) than studies in LMICs (3.55
28 days; 95% CI 0.84-6.26; $p = 0.01$) (Figure 4).

29 Studies with non-invasive infections reported a WMD of 2.19 days (95% CI: 1.56-2.81;
30 $p < 0.001$), which decreased from 7.66 (95% CI: 5.83-9.46; $p < 0.001$) in 2000-2009 to 1.44
31 (95% CI: 0.77-2.10; $p < 0.001$) in 2010-2018 (online supplementary figure 7).

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3 1 The data on ICU-LOS were provided in 7 studies and showed that BSIs caused by ESBL
4 2 producers had a WMD of LOS of 3.07 days (95% CI: 1.61-4.54; $p < 0.001$).

6
7 3 Heterogeneity of the studied effect-modifiers did not reach statistical significance when
8 4 assessed by metaregression (supplementary table S6). Sensitivity analysis based on the quality
9 5 of studies revealed no notable difference in the effect estimates after exclusion of low-quality
10 6 studies (data not shown). Egger's test and the funnel plots (online supplementary figure 1 and
11 7 2) showed evidence for small study effects ($p < 0.001$) and publication bias.

16 8 **DISCUSSION**

18 9 This systematic review shows that ESBL production has a significant impact on the most
19 10 relevant patient-related clinical outcomes. In the subgroup analyses, all-cause mortality,
20 11 attributable mortality, and LOS both in hospital and in ICU were higher for patients with BSIs
21 12 due to ESBL-producing *Enterobacteriaceae* than for patients with BSIs due to non-ESBL-
22 13 producing strains. Non-invasive infections caused by ESBL-producing strains were associated
23 14 with higher all-cause mortality and prolonged LOS. Within the limitation of the low number
24 15 of studies evaluating specific patient populations, paediatric and cancer patients seemed to
25 16 suffer a higher impact of ESBL invasive infections than the overall population. Stratifying by
26 17 pathogen type, the impact of ESBL production was higher for *E. coli* BSIs than for *K.*
27 18 *pneumoniae* BSIs. No relevant differences in mortality analysis emerged with stratification by
28 19 study design or country income level. Impact of ESBL infections on mortality became more
29 20 evident in more recent studies. Studies reporting on appropriateness of empirical therapy,
30 21 ESBL resistance mechanisms, and MICs showed a higher clinical impact of ESBL infections
31 22 than studies not assessing these variables. In particular, pooled ORs adjusted for inappropriate
32 23 empirical treatment, showed a remarkably higher OR for mortality in patients with ESBL
33 24 infections.

34 25 Our findings confirm the results of previous systematic reviews. Schwaber et al. performed a
35 26 systematic review comparing mortality in ESBL BSIs and non-ESBL BSIs in studies
36 27 published through 2003.² The authors show a pooled RR for all-cause mortality of 1.85 but, in
37 28 contrast to our study, they combined *E. coli*, *Klebsiella* spp., and *Proteus* spp. in the analysis
38 29 because of sample size limitations. Rottier et al. analysed studies published through 2010 and
39 30 adjusting results for inappropriate empirical treatment found an adjusted OR of 1.37.³ Our
40 31 study, adding more than 50 studies in 17 years to the Rottier systematic review, confirmed the
41 32 clinical importance of ESBL production to all-cause mortality and for the first time assessed
42 33 the role of ESBL production on attributable mortality. We addressed relevant effect-modifiers

1 through subgroup analyses and found that population, pathogen, and assessment of empiric
2 therapy all had an impact on estimates. Because we believe that appropriate empirical
3 treatment plays a relevant role in invasive infections, we performed a secondary analysis by
4 pooling only adjusted ORs and confirming the significant impact of antibiotic resistance as
5 already shown in a previously published systematic review.⁹⁷ The lack of consideration of
6 appropriateness of therapy in the studies evaluating mortality seems to underestimate the
7 impact of ESBL production on mortality. However, studies assessing the impact of
8 appropriate therapy did not provide homogeneous definition and could refer either to
9 empirical or definite therapy or a single component irrespective of the dosage, making results
10 difficult to interpret. Especially in infections with different sources and different clinical
11 severity, the sole contribution of empirical therapy remains challenging to measure. For
12 example, patients with UTI receiving inappropriate empirical antibiotic therapy can
13 potentially show a favourable outcome, most probably due to the high concentration of
14 antibiotic reached in the urinary tract.⁹⁸

15 Community acquired ESBL infections emerged in the late 1990s and show an increasing
16 trend.^{99,100} Recent study shows that community onset ESBL infections are associated with
17 lower mortality compared with healthcare associated and hospital acquired infections.¹⁰¹ The
18 place of acquisition could not be appropriately addressed in our meta-analysis due to the lack
19 of data in included studies.

20 Our systematic review contributes to the discussion on the limitation of current evidence for
21 the estimation of mortality due to antibiotic-resistant infections. The impact of ESBL
22 production on LOS in our study has shown that both BSIs and non-invasive infections lead to
23 prolongation of hospitalisation.

24
25 Our study has some limitations. Although results of the meta-analyses were significant in all
26 the subgroups, we could analyse only a limited number of studies providing information for
27 subgroups such as haematological patients and low-income countries, making generalizability
28 of results less certain for these specific patient populations. Only a few studies reported MIC
29 data or specific ESBL molecular resistant phenotype (i.e., AmpC). Moreover, publication bias
30 was detected in both the main analyses (all-cause mortality and LOS), thus implying the
31 possibility that results from small studies with non-significant results might have been
32 conducted and not published, resulting in a possible overestimation of our results. The non-
33 homogeneous reporting of some relevant data in published literature (e.g., infection type,

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3 1 presence of bacteremia, disease severity, underlying comorbidities and resistance mechanism)
4 2 may also have affected the precision of the estimate. A limited number of patients with non-
5 3 bacteremic infections was included in our systematic review, thus limiting the generalizability
6 4 of results to this patients' population. Moreover, patients with ESBL are intrinsically at higher
7 5 risk of mortality and complications because they are often older, have more comorbidities or
8 6 higher antibiotic exposure, and are at higher risk of receiving inappropriate empirical
9 7 treatment.¹⁰² Finally, due to resource constraints, we had to limit our search to PubMed
10 8 database with the chance of missing relevant studies.

11 9 In summary, our systematic review emphasises the importance of suspicion and confirmation
12 10 of ESBL production as soon as possible for invasive infections and demonstrates that ESBL
13 11 production increases the risk of attributable mortality and LOS in both hospital and ICU for
14 12 invasive and non-invasive infections. Patients with ESBL infections remain at higher risk of
15 13 mortality and prolonged LOS even after adjustment for empiric inappropriate treatment.
16 14 Control for other relevant effect-modifiers is hindered by the sparseness of published data.
17 15 Individual patient data (IPD) network meta-analyses are needed to define differences in
18 16 outcomes between severe intravascular infections and bacteremia. Future studies addressing
19 17 the clinical burden of drug-resistant infections must include ESBL production and should
20 18 assess both the impact of molecular mechanisms of resistance and effect on specific patient
21 19 populations such as haematological patients and those in LMIC.

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24 22 **Author Contributions** ET contributed to the study concept. BPG and PS performed data
25 23 analysis. PS and AC extracted data and wrote the first draft of the manuscript. DL contributed
26 24 to the first draft of the manuscript. EC and ET wrote the final version of the manuscript. CB
27 25 reviewed the paper. All authors read, edited, and approved the final manuscript. The
28 26 corresponding author had full access to all the data in the study and had final responsibility
29 27 for the decision to submit for publication.

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34 32 paper for publication.

35 33 **Competing interests** The authors report no competing interests.

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3 **Data sharing statement** Requests for data should be addressed to the corresponding author.

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3 **1 FIGURE LEGENDS**

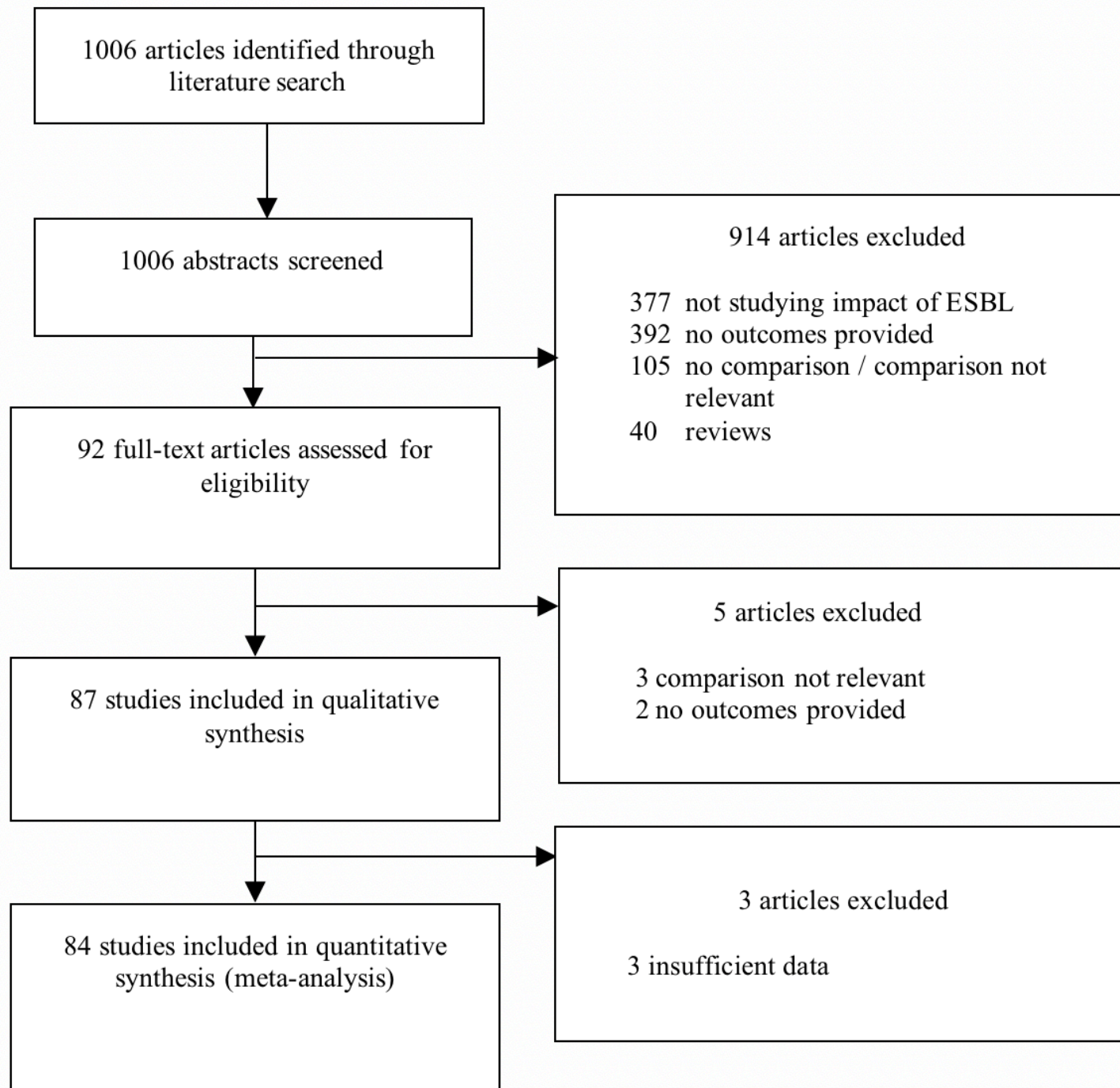
4 2
5 3 Figure 1: Literature search and study inclusion and exclusion

6 4
7 5 Figure 2: Pooled risk ratios for all-cause mortality in patients with ESBL bloodstream
8 6 infections compared to patients with non-ESBL bloodstream infections— subgroups not
9 7 included in attributable mortality

10 8
11 9 Figure 3: Pooled risk ratios for attributable mortality in patients with ESBL bloodstream
12 10 infections compared to patients with non-ESBL bloodstream infections

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14 12 Figure 4: Weighted mean difference in the length of stay for patients with ESBL bloodstream
15 13 infections compared to patients with non-ESBL bloodstream infections

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risk ratio (95% CI)

Category

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Overall

Overall 56 1.70 (1.52, 1.90)

Mortality time

14 day mortality 5 1.77 (1.15, 2.72)

28 day mortality 22 1.63 (1.35, 1.97)

Time not defined 27 1.70 (1.47, 1.97)

Income classification

High income countries 41 1.76 (1.54, 2.00)

Low/middle income countries 15 1.56 (1.25, 1.96)

Study population

All kinds of patients 36 1.65 (1.43, 1.90)

Cancer patients 5 1.73 (1.16, 2.57)

Children 7 2.09 (1.62, 2.71)

Neonates 3 1.76 (1.27, 2.45)

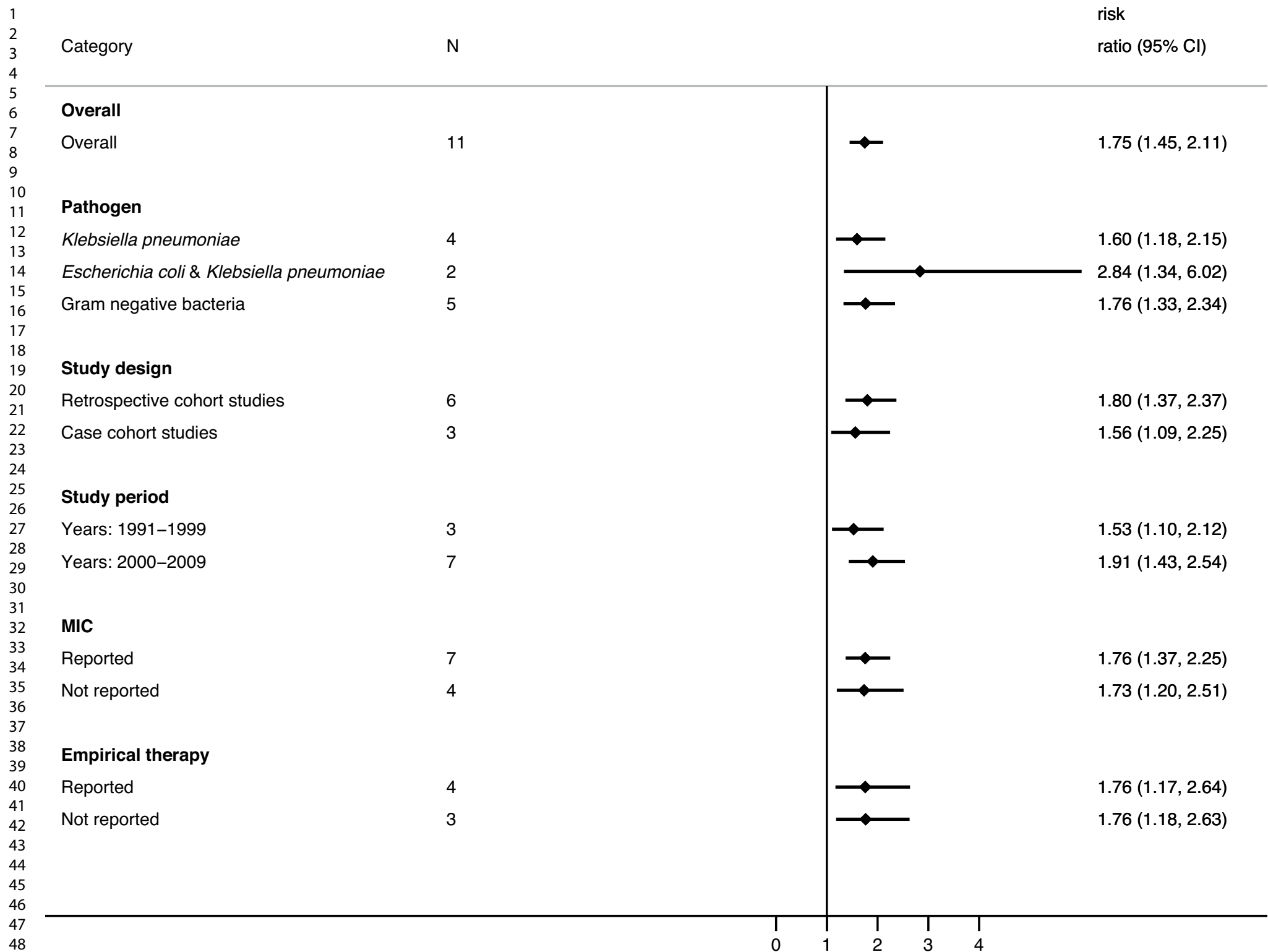
Appropriateness of therapy

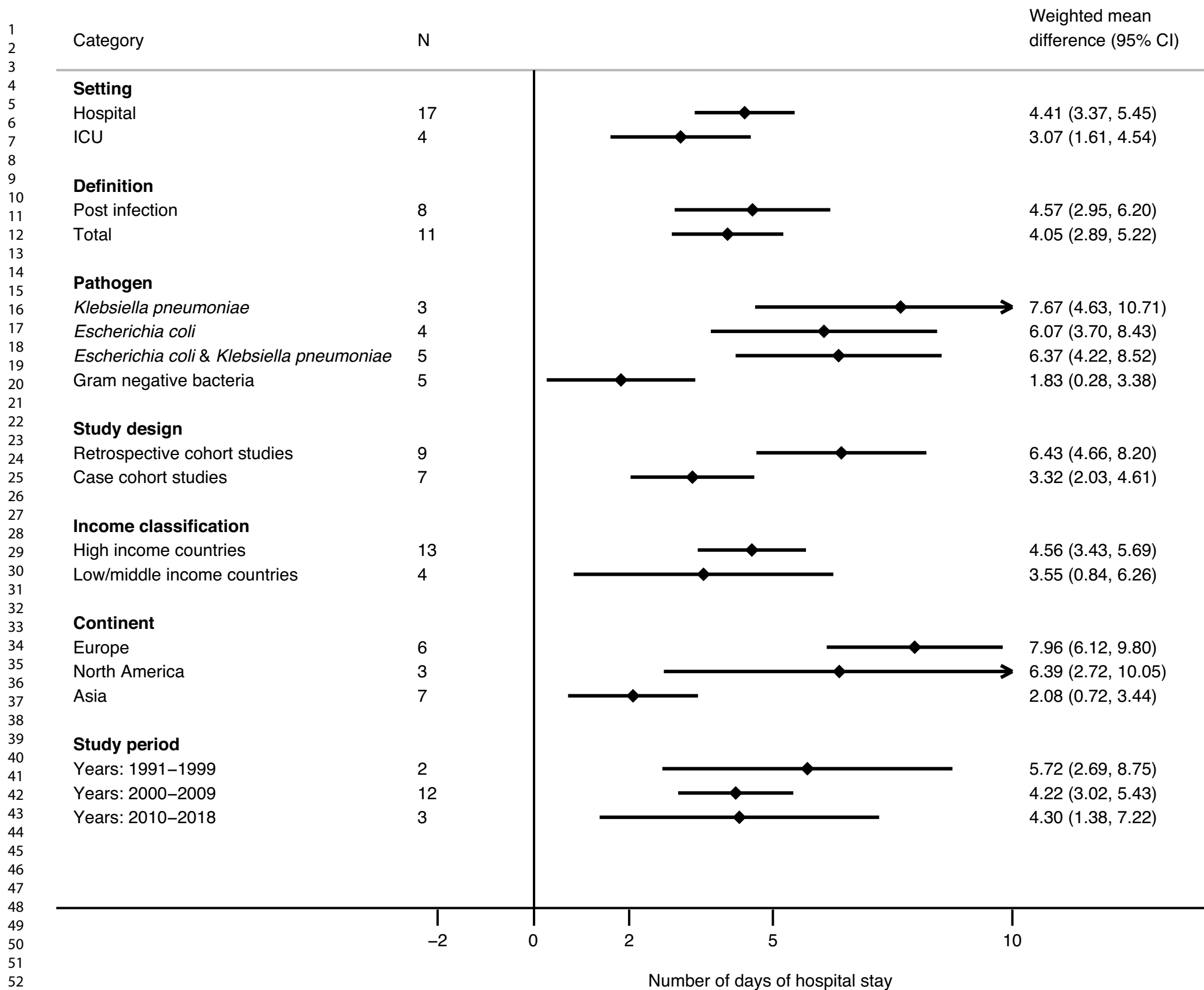
Reported 44 1.75 (1.54, 1.99)

Not reported 12 1.55 (1.26, 1.90)

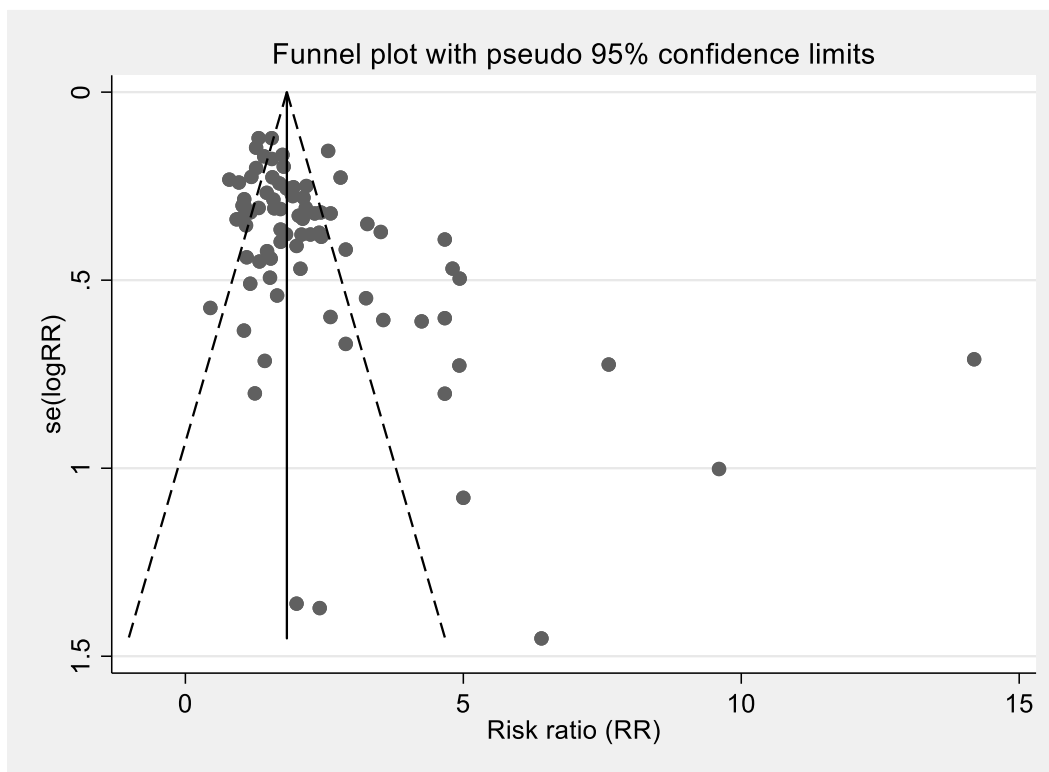
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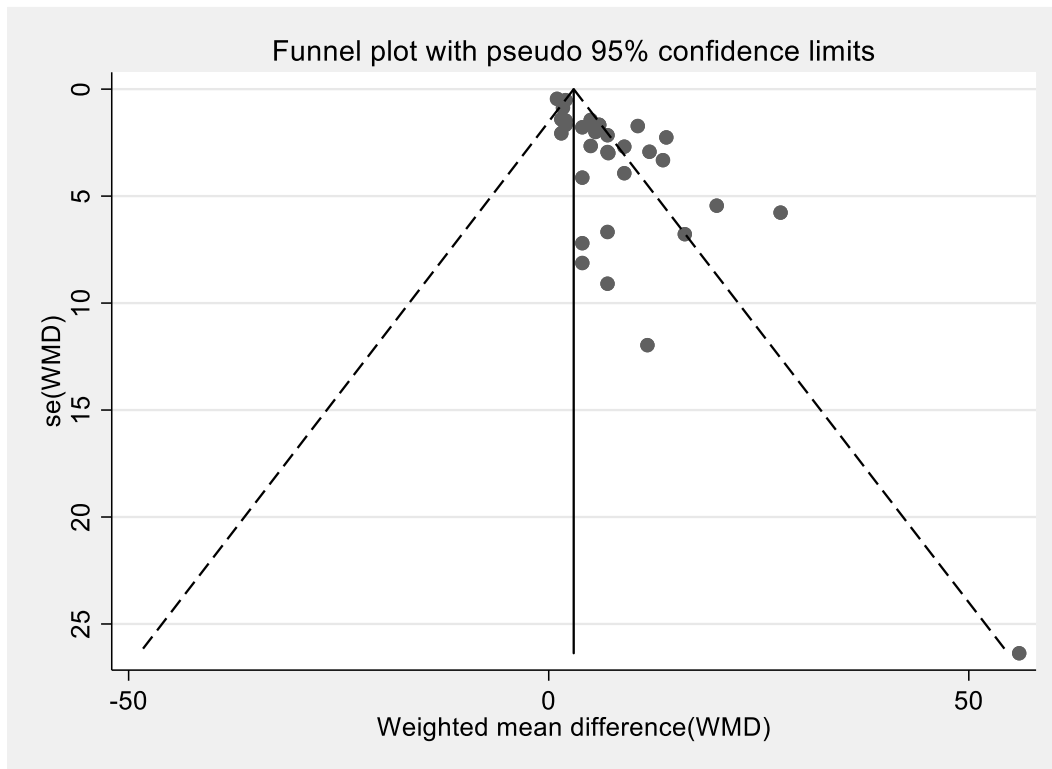


Supplementary figure 1: Funnel plot of risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections



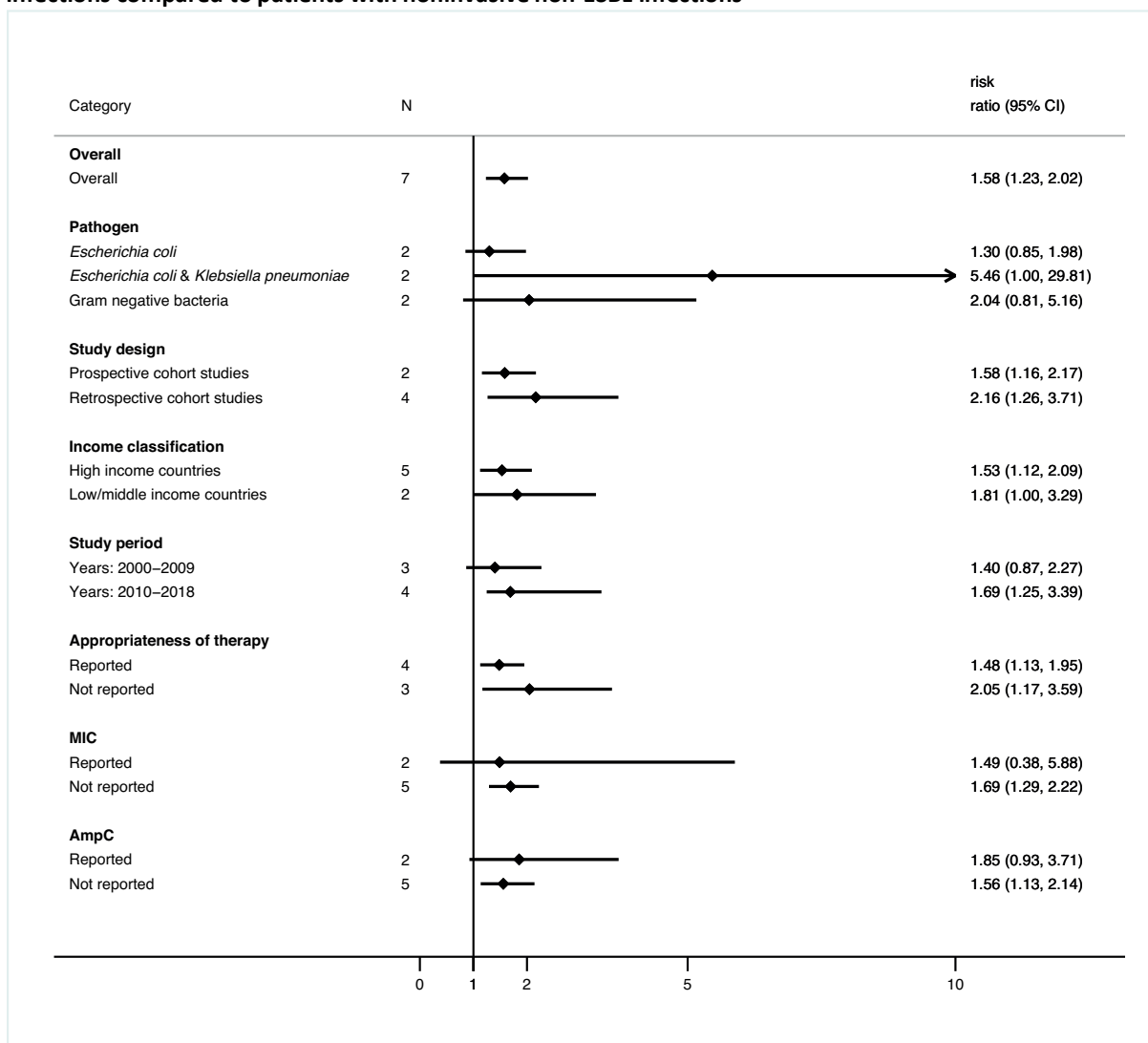
The y axis $se(\log RR)$ is the standard error of the log risk ratio Pseudo 95% confidence limit refers to the 95% confidence limits around the summary treatment effect for each standard error on the vertical axis and to the expected distribution of studies in the absence of heterogeneity or of selection biases.

Supplementary figure 2: Funnel plot of weighted mean differences in the length of stay for patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections



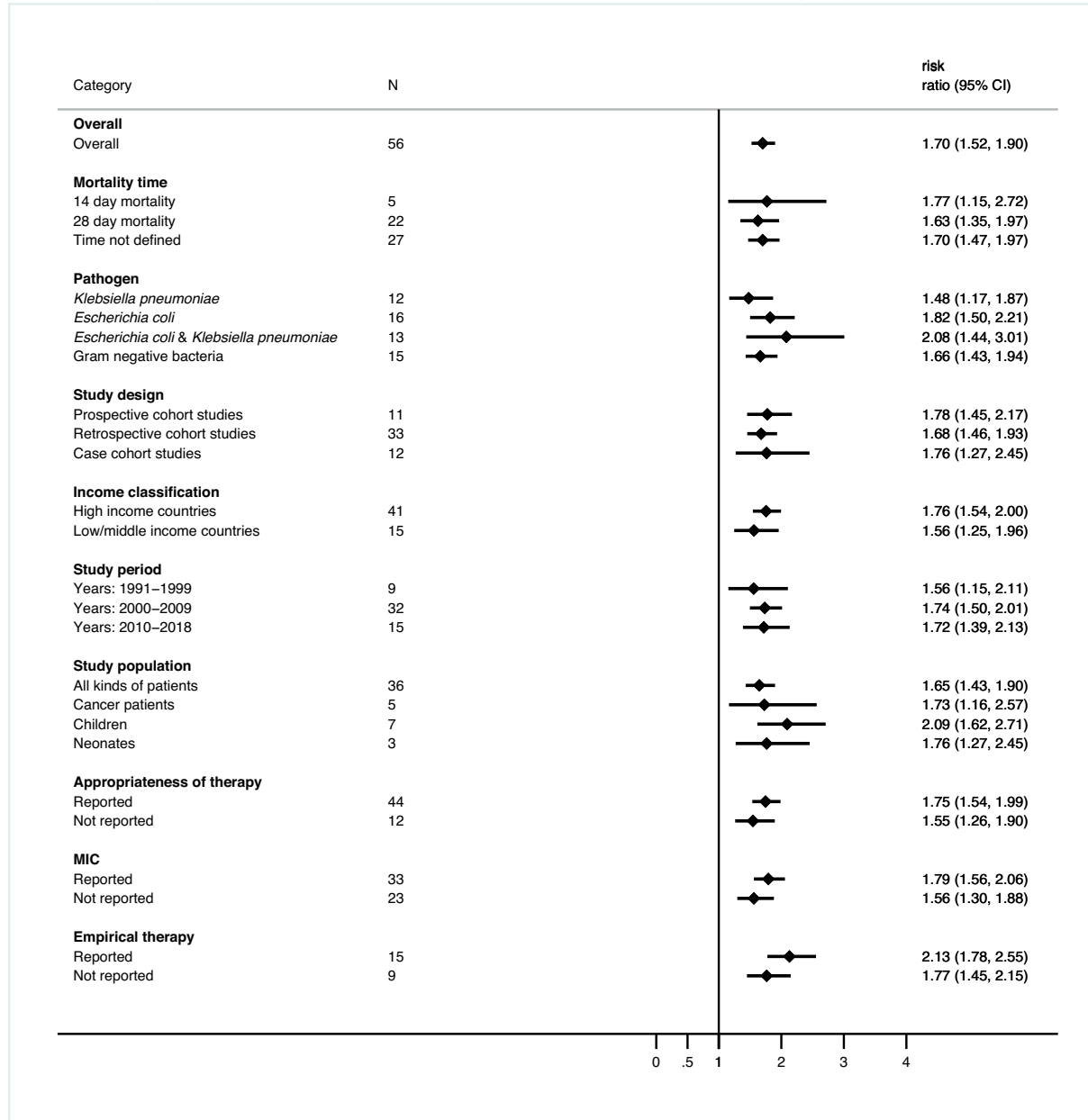
The y axis $se(WMD)$ is the standard error of the weighted mean difference. Pseudo 95% confidence limit refers to the 95% confidence limits around the summary treatment effect for each standard error on the vertical axis and to the expected distribution of studies in the absence of heterogeneity or of selection biases.

Supplementary figure 3: Pooled risk ratios for all-cause mortality in patients with noninvasive ESBL infections compared to patients with noninvasive non-ESBL infections

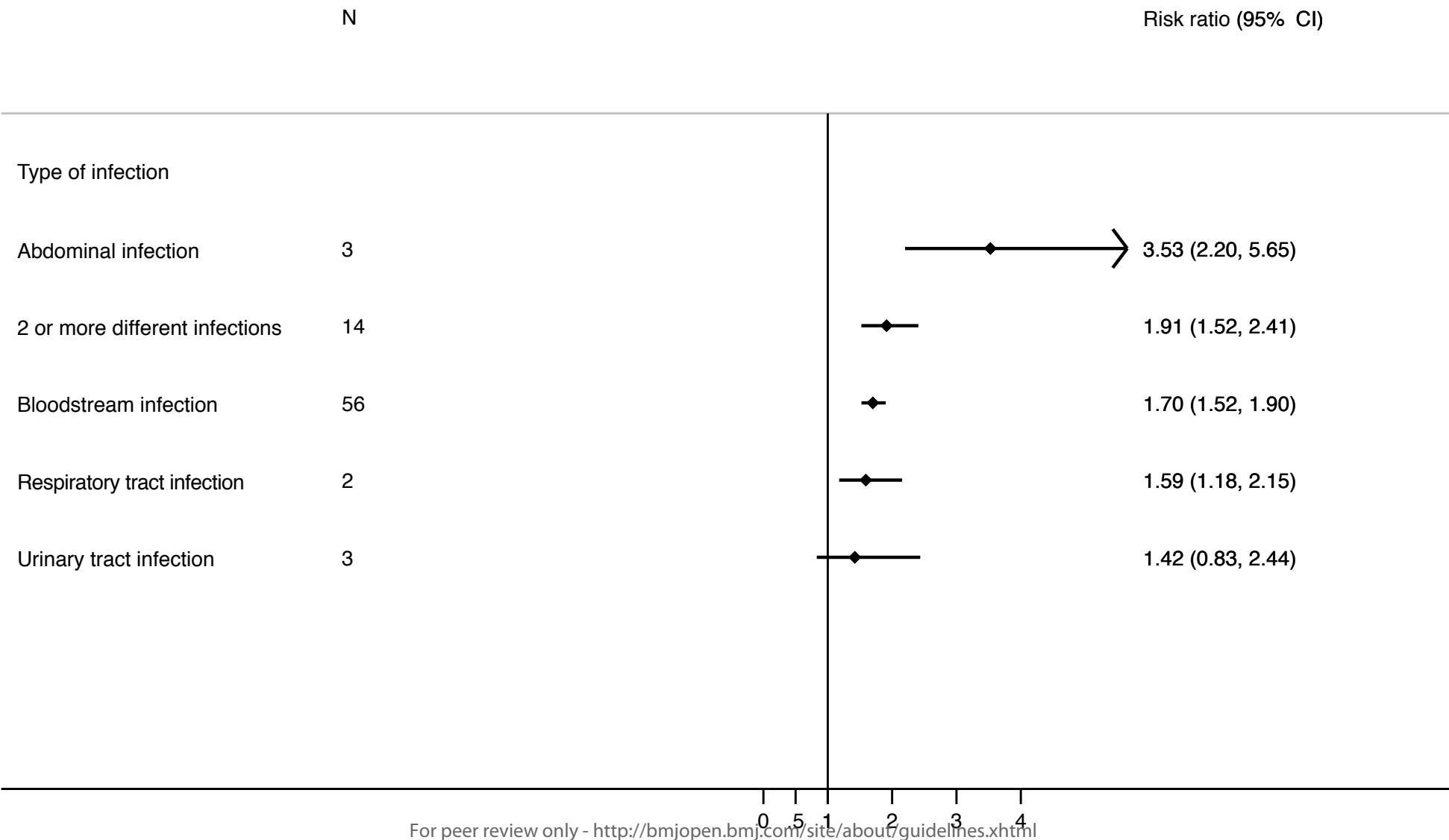


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Supplementary figure 4: Pooled risk ratios for all-cause mortality in patients with ESBL bloodstream infections compared to patients with non-ESBL bloodstream infections—all subgroups



Supplementary figure 5: Pooled risk ratios for all-cause mortality stratified by type of infection

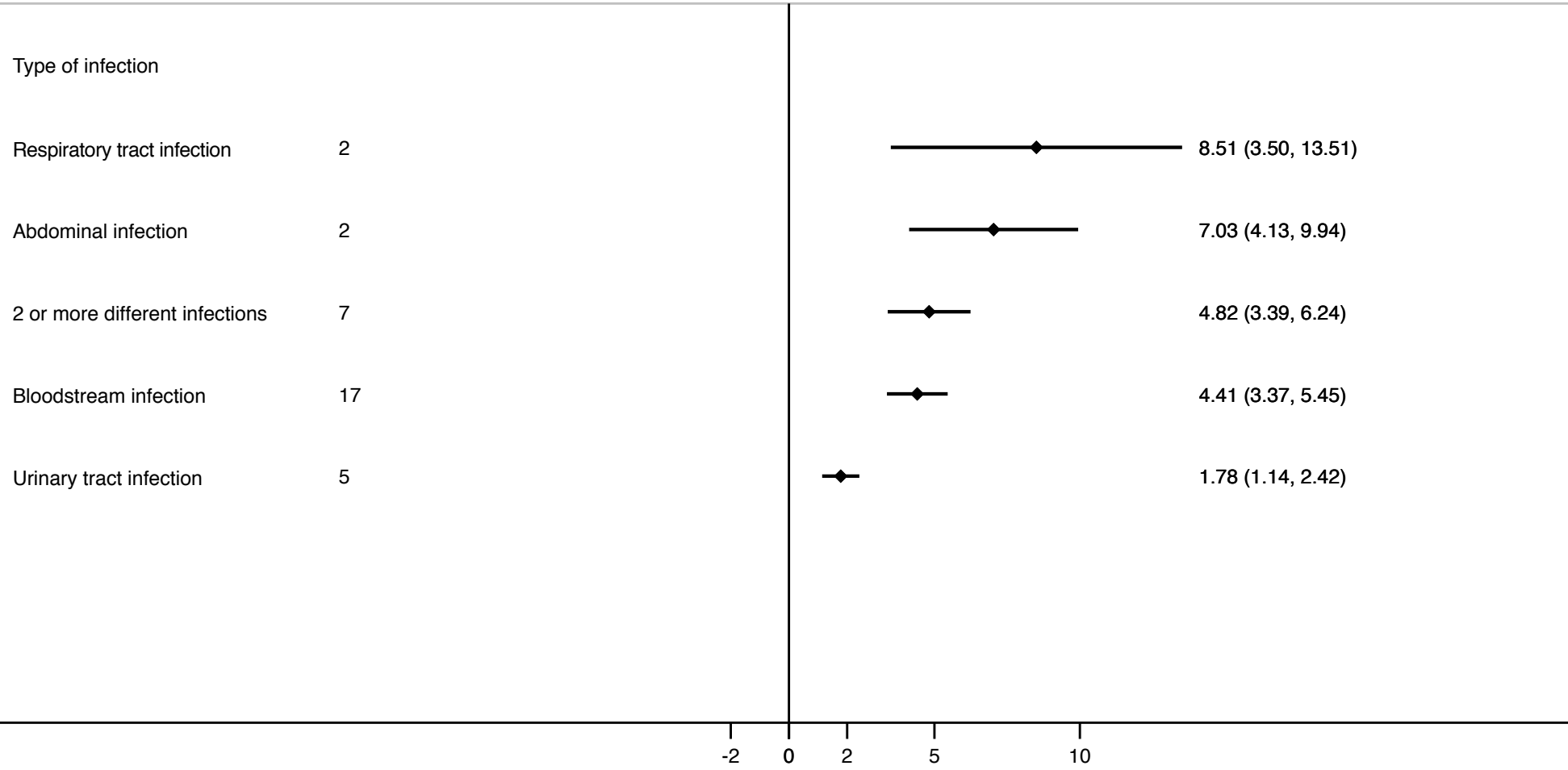


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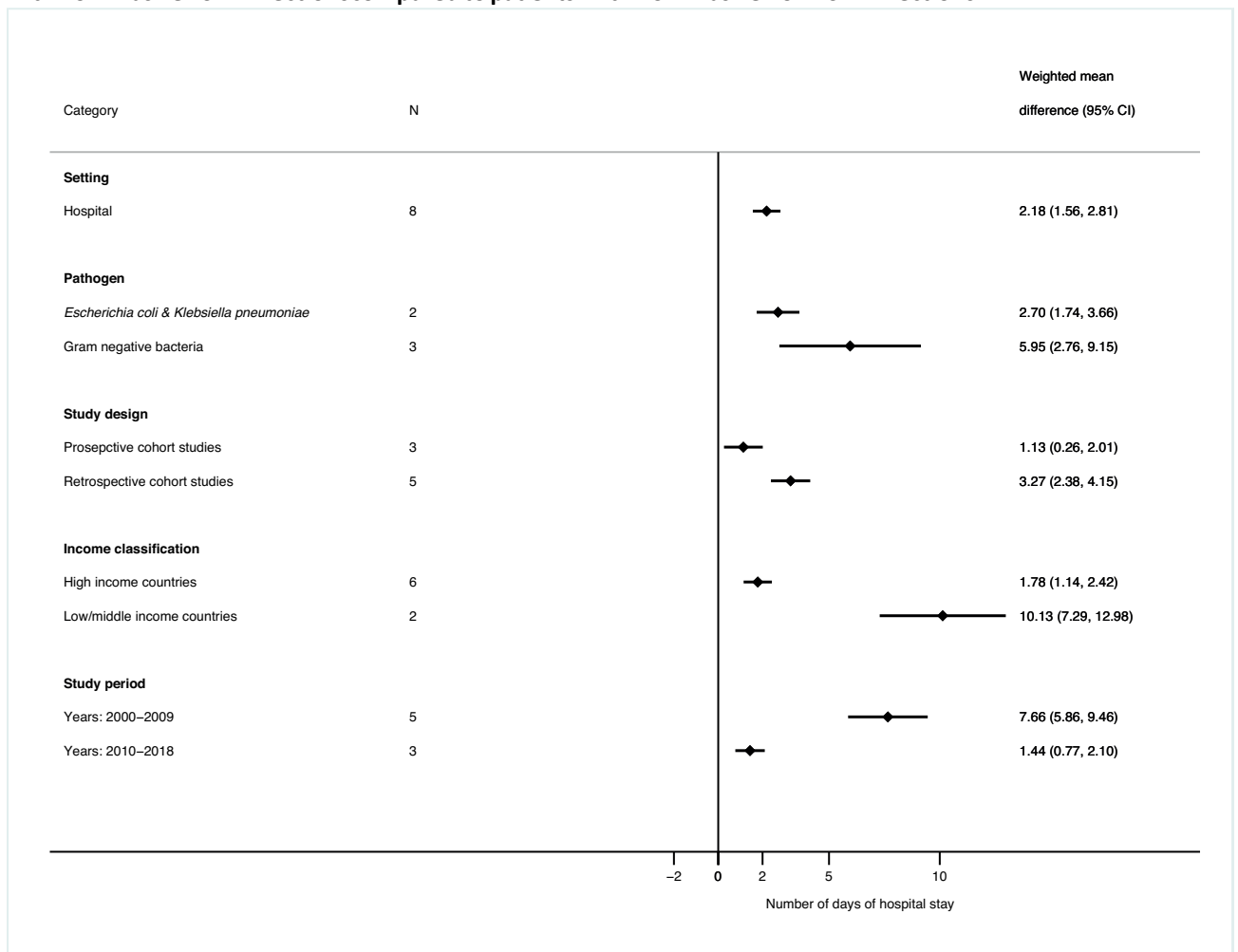
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Supplementary figure 6: Weighted mean differences in length of hospital stay stratified by type of infection

N Weighted mean difference (95% CI)



Supplementary figure 7: Weighted mean differences in length of hospital stay in patients with noninvasive ESBL infections compared to patients with noninvasive non-ESBL infections



Supplementary table S1: Search terms used in PubMed :

((ESBL[tw] OR ""Extended spectrum beta-lactamase""[tw] OR ESBL[Mesh] OR ""Extended spectrum beta-lactamase"" [Mesh]) OR Extended spectrum ? lactamase[tw] OR Extended spectrum ? lactamase[Mesh])

AND

(Escherichia Coli[Mesh] OR E.coli[Mesh] OR Escherichia Coli[tw] OR E.coli[tw])) OR (Klebsiella pneumoniae[Mesh] OR K.Pneumoniae[Mesh] OR Klebsiella pneumoniae[tw] OR K.Pneumoniae[tw])

Coupled with

(length of stay[mesh] OR (hospitalisation[tw] AND length[tw]) OR length of hospitalisation[tw] OR length of hospitalization[tw] OR duration of hospitalization[tw] duration of hospitalisation[tw] OR LOS[tw] OR ((period[tw] OR length[tw]) AND (hospital stay[tw] OR hospitalisation[tw] OR hospitalization[tw])) OR

(mortality[mesh] OR mortality[tw] OR death rate[tw] OR fatality[tw] OR survival rate[tw] OR death[tw] OR died[tw] OR dead[tw])) OR

(cost*[Title/Abstract] OR "costs and cost analysis"[MeSH:noexp])

Coupled with

("0001/01/01"[PDat] : "2018/10/01"[PDat])

Supplementary table S2: Modified Newcastle Ottawa quality assessment scale for case-control studies and cohort studies.

For case cohort studies, the quality criteria assessed are			
1	Is the case definition adequate?	a*	yes, with independent validation
		b	yes, eg. record linkage or based on self-report
		c	no description
2	Representativeness of the cases	a*	consecutive or obviously representative series of cases
		b	potential for selection biases or not stated
3	Selection of Controls	a*	community controls
		b	hospital controls
		c	no description
4	Definition of Controls	a*	no history of disease (endpoint)
		b	no description of source
5	Comparability of cases and controls on the basis of the design or analysis	a*	study controls for at least one variable (including age, sex and comorbidities)
		b**	study controls for more than one variable (including age, sex and comorbidities)
6	Ascertainment of exposure	a*	secure record (eg surgical records)
		b	structured interview blind to case/control status
		c	interview not blinded to case/control status
		d	written self-report or medical record only
		e	no description
7	Same method of ascertainment for cases and controls	a*	yes
		b	no
		c	unclear
8	Non-Response rate	a	same rate for both groups
		b	non respondents described
		c	rate different and no designation
For cohort studies, the quality criteria assessed are			
1	Representativeness of the exposed cohort	a*	truly representative
		b*	somewhat representative
		c	selected group of users
		d	no description
2	Selection of the non-exposed cohort	a*	drawn from the same community as the exposed cohort
		b	drawn from a different source
		c	no description of the derivation of the non-exposed cohort
3	Ascertainment of exposure	a*	secure record (eg surgical records)
		a*	structured interview
		c	written self-report
		d	no description
4	Demonstration that outcome of interest was not present at start of study	a*	yes
		b	no
		c	unclear
5	Comparability of cohorts on the basis of the design or analysis	a*	study controls for age or comorbidities
		b**	study controls for age and comorbidities
6	Assessment of outcome:	a*	independent blind assessment
		b*	record linkage
		c	self-report
		d	no description

7	Follow-up long enough for outcomes to occur	a*	yes
		b	no
		c	unclear
8	Adequacy of follow up of cohorts	a*	complete follow up – all that matters subjects accounted for, subjects lost to follow up unlikely to introduce bias - small number
		b*	inadequate numbers but description provided of those lost
		c	inadequate follow up rate and no description of those lost
		d	no statement

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

EW Only

Supplementary table S3: Study characteristics overview

Subgroup	All Studies	Bloodstream infections	Noninvasive infections
	87	57	10
Country			
South Korea ^{13,14,16,17,31,35,38,42,44,46,51,52,57,59}	14	9	2
Thailand ^{24,26,45,53-55,88}	7	3	
USA ^{10,18,28,32,48,61,69}	7	2	1
Spain ^{36,40,58,62,70,91,93}	7	4	2
Taiwan ^{12,39,64,71,82,84,96}	7	5	2
China ^{60,73,74,76,86}	5	4	
Israel ^{23,47,92,93}	4	3	
Germany ^{10,40,43,63}	4	3	
Italy ^{25,33,37}	3	3	
Japan ^{76,81,86}	3	3	
Tanzania ^{19,66,75}	3	3	
India ^{49,50,80}	3	1	1
Canada ^{65,67,85}	3	2	
UK ^{22,30,89}	3	3	
France ^{68,79}	2	1	1
South Africa ^{13,81}	2	1	
Brazil ^{21,34}	2	2	
Greece ⁹⁰	1	1	
Hungary ⁹⁵	1	1	
Lebanon ²⁷	1	-	
Malaysia ²⁹	1	-	1
Mexico ⁷²	1	1	
Saudi Arabia ²⁰	1	1	
Turkey ⁷⁸	1	1	
Continent			
Asia ^{12-14,16,17,20,23,24,25,27,29,31,35,38,39,42,44-47,49, 55,57,59,60,64,71,73,74,76,80-82,84,86-88,92,93,96}	46	29	6
Europe ^{11,22,25,30,33,35,37,40,41,43,58,62,63,68,70,78,79,89-91,94,95}	22	17	3
North America ^{10,18,28,32,48,61,65,67,69,85}	10	4	1
Africa ^{15,19,66,75,83}	5	4	-
South America ^{21,34,72}	3	3	-
More than 1 continent ⁵⁶	1	-	-

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Income group			
High-income countries ^{10-14,16-18,20,22,23,25,28,30-33,35-44,46-48,51,52,57-59,61-65,67-71,76,79,81,82,84-86,89-96,}	60	41	8
Low- and middle-income countries ^{15,19,21,23,25,27,29,34,45,50,53-55,60,66,72-75,77,78,80,83,87,88}	26	16	2
High-income countries AND Low- and middle-income countries ⁵⁶	1	-	-
Study design			
Case cohort study ^{10,12,24-28,31,40,44,46,55,58,61,63-65,67-69,85-87}	24	14	
Retrospective cohort study ^{11,13-17,20,21,23,29,33-38,41-43,45,47,48,50-54,59,60,71,73,74,76-78,81-84,88,89,93,95,96}	44	32	
Prospective cohort study ^{18,19,30,32,39,49,56,62,66,70,72,75,79,80,90-92,94}	18	11	
Year group			
1991-1999 ^{10,60,15,16,17,62,21,25,28,36,46,93,94}	13	10	-
2000-2009 ^{11-14,18-20,22-24,26,27,29-35,37-45,47,49-52,54,55,57,58,61,63,64,67-69,89-92,95,96}	49	31	6
2010-2018 ^{48,53,54,59,65,66,70-88}	25	16	4
Pathogen			
<i>Escherichia coli</i> ^{11,24,30,33,35-37,40,43,45,52,55,58,59,68,70,71,73,76,86,87,91,94}	23	16	3
<i>Klebsiella pneumoniae</i> ^{15,16,20,21,25,29,32,34,41,43,47,61,62,74,78,83,95,96}	17	11	1
<i>E. coli</i> and <i>K. pneumoniae</i> ^{10,13,14,17,26,28,38,43,44,46,48,50,51,54,57,60,63,69,85,88,89}	20	13	2
Gram-negative bacteria ^{12,18,19,22,23,27,31,39,42,49,53,56,64-67,72,75,77,79-82,84,90,92,93}	27	17	4
Study setting			
Entire hospital ^{10,11,16,18,20-27,29,30,33-38,40-46,48-50,52-55,58-60,62,65-69,73,74,76,82,85,86,90-96}	57	40	7
Intensive care unit ^{32,61,64,75,79-81,88,89}	9	5	1
Pediatric ward ^{17,19,28,51,57,78,83,88}	8	7	-
Neonatal ward ^{15,61,64,71,75}	5	3	-
Neonatal intensive care unit ^{61,64,75}	3	2	-
Medical ward ^{13,39,70}	3	-	2
Not provided ^{31,47}	2	-	-
Emergency Department ^{12,84}	2	2	-
Surgical ward ^{32,56}	2	-	-
Burn unit ³²	1	-	-
Oncology ⁷²	1	1	-
Referral centre for hepatopancreaticobiliary diseases ⁷⁷	1	-	-
Hematological ¹⁴	1	1	-

Study population			
All kinds of patients ^{10-13,14,18,20-27,29,30,34,35,39-41,43-46,48-50,52-56,58,60,62,63,65-69,76,82,84-86,90,92-95}	55	36	7
Intensive care unit patients ^{32,79-81,87,89}	6	3	1
Children ^{17,19,28,51,57,78,83,88}	8	7	-
Neonates ^{15,61,64,71,75}	5	3	-
Cancer patients ^{33,51,59,72,91}	5	5	-
Immunocompromised patients ⁵¹	1	1	-
Diabetic patients ⁹⁶	1	1	-
Elderly patients ⁷⁰	1	-	1
Patients with chemotherapy/stem cell transplantation ^{14,91}	2	2	-
Patients after prostatitis biopsy ⁴²	1	-	1
Lungs transplantation patients ⁴⁷	1	-	-
Hematological patients ⁷³	1	1	-
All except cardiothoracic therapy, transplant surgery, burns ⁷⁴	1	1	
Patients with pyogenic liver abscess ⁷⁷	1	-	-
Data reported			
Treatment information ^{10,12-13,23-25,30-38,40,44-49,51,52,54-65,67,68,70-96}	74	50	6
Appropriateness of treatment ^{10,12-14,16,17,19-21,23-26,30-38,40,44-46,48,49,51,52,54-56,58-60,62-65,67,68,70,72-74,76,77,79,81,83-86,89-96}	62	45	5
Empirical therapy ^{14,16,17,24,25,33,35-38,40,44,51,52,56,58,59,63,76,81,83,94}	22	16	2
Treatment outcome ^{10,12-21,25,26,30-38,40,44-49,51,52,54-57,59-65,67,68,72-74,76,78-81,83-86,88-92,94-96}	64	45	3
Minimum inhibitory concentration results ^{10,11,13,14,16-19,22-25,27,28,32,33,35-41,43,44,47,50-52,54-59,62,63,66,68,69,76-78,80,81,83,85-87,89,94,95}	52	34	4
AmpC genotyping ^{10,11,17,32,41,46,50,56,57,65,66,70,86}	13	6	2

Supplementary table S4: Characteristics for each study

	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Lautenbach E ¹⁰	1997-1998	USA	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality; LOS	Risk factors for infection with ESBL-producing pathogens, difference in clinical outcomes of infections: resistant vs. susceptible organisms	EC, KP
Kim SH ¹⁴	2007-2008	South Korea	Cohort study, Retrospective	Non-ESBL-infection	Patients who received either chemotherapy or stem cell transplantation; neutropenic fever	Hematological ward, Others	All-cause mortality (28 day)	Risk factors for acquisition of ESBL, appropriateness of empirical antimicrobial therapy, clinical outcomes in relation to ESBL production	EC, KP
Chayakulkeere M ⁵³	2015-2015	Thailand	Cohort study, Retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Prevalence & risk factors for infections with & antibiotic susceptibility patterns of & outcomes of patients infected with ESBL-producing-GNB	GNB
Pisarntharak A ⁵⁴	2003-2007	Thailand	Cohort study, Retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Predictors for mortality associated with community-onset BSI with ESBL-producing pathogens, initial empirical antimicrobial regimens, associated hospital resource utilisation, costs accrued after diagnosis of BSI	EC, KP
Pisarntharak A ⁵⁵	2003-2004	Thailand	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Mortality associated with community-onset infection due to ESBL-producing pathogens, associated hospital resource use, post-infection hospital cost	EC
Jean SS ⁵⁶	2010-2011	Portugal, Columbia, the Philippines, Taiwan, Thailand	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Surgical ward	Attributable mortality, LOS	Clinical impact on hospitalised patients with community-acquired complicated intra-abdominal infection: ESBL-producing- vs. non-ESBL-producing pathogens	GNB
Lee J ⁵⁷	1999-2005	South Korea	interventional studies	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality (28 day)	impact of a change in antibiotic policy on ESBL-prevalence	EC, KP
Briongos-Figuero A ⁵⁸	2009-2010	Spain	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Characteristics & associated risk factors for EBSL-enterobacteria-UTIs	EC
Ha YE ⁵⁹	2010-2012	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients with cancer	Entire hospital	All-cause mortality (28 day)	Clinical & molecular epidemiology of ESBL-EC bacteraemia, clinical impact of ESBLs on patient outcome	EC
Du B ⁶⁰	1997-1999	China	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors for nosocomial ESBL-EC- and ESBL-KP- bacteraemia & influence on patient outcome.	EC, KP

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Stone PW ⁶¹	2001	USA	Case cohort study	Non-ESBL-infection	Neonates at NICU	NICU	LOS	costs of interventions aimed at controlling the outbreak, attributable length of stay associated with infection and colonisation with ESBL-KP	KP
Pillay T ¹⁵	1995-1996	South Africa	Cohort study, retrospective	Non-ESBL-infection	Neonates	Neonatal ward	All-cause mortality	Use of piperacillin/tazobactam in treatment of KP- infection	KP
Kim BN ¹⁶	1999-2000	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, LOS	Prevalence & clinical characteristics of ESBL-KP- bacteraemia, impact of ESBL- production on outcome of patients with KP- bacteraemia in endemic situation.	KP
Kim YK ¹⁷	1993-1998	South Korea	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality	Risk factors & clinical outcomes & clinical responses to treatment of ESBL-EC- and ESBL-KP-bacteraemia, prevalence and types of their ESBLs	EC, KP
Bhavnani SM ¹⁸	2001-2002	USA	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Risk factors for occurrence of invasive ESBL-EC- and ESBL-KP-infections, factors associated with clinical outcome, drug regimens for treatment of infections associated ESBL/non-ESBL strains in real-life clinical practice, clinical response rates for patients treated with cephalosporins/other classes of antimicrobial agents, /carbapenems, clinical response for those patients with infection associated with ESBL and non-ESBL-producing strains with MIC values V8 Ag/mL treated with cephalosporins.	GNB
Blomberg B ¹⁹	2001-2002	Tanzania	Cohort study, prospective	Non-ESBL-infection	Neonates, children	Pediatric ward	All-cause mortality	Prevalence & clinical implications of ESBL production in EC-,KP-, Salmonellae- septicemia	GNB
Pená C ⁶²	1993-1995	Spain	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Clinical epidemiology& outcome of ESBL-KP- bacteraemia, relevance of ESBL strains in mortality of patients with hospital-acquired KP-BSI.	KP
Kola A ⁶³	2002-2004	Germany	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS, ICU-LOS	Outcomes of ESBL-EC- and ESBL-KP-infections	EC, KP
Isai MH ⁶⁴	2001-2012	Taiwan	Case cohort study	Control group: non-ESBL-infection, second control group: all hospitalised patients	Neonates at NICU	NICU	Attributable mortality, all-cause mortality, LOS	Clinical features& risk factors& molecular epidemiology of ESBL-GNB	GNB
Maslikowska JA ⁶⁵	2010-2013	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS	Differences in clinical & microbiological outcome, mortality, and/or hospital resource use: ESBL-EC- and ESBL-Ks- vs non-ESBL-EC- and non-ESBL-Ks-infections	GNB

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Onken A ⁶⁶	2012-2013	Tanzania	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Most common bacterial pathogens causing BSI, antimicrobial susceptibility	GNB
Nguyen ML ⁶⁷	2005-2010	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS, ICU-LOS	Risk factors for & patient outcomes associated with ESBL-EC- and ESBL-Ks- bacteraemia, appropriateness of empiric antibiotic therapy & effect of inappropriate empiric therapy on outcomes	GNB
Denis B ⁶⁸	2005-2009	France	Case-control study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day), LOS	Prevalence & risk factors for ESBL-EC bacteraemia, impact on length of stay & 30day mortality	EC
Chopra T ⁶⁹	2004-2009	USA	Case cohort study	Case 2(Control1): non-ESBL-infection, second control group: no infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Predictors of ESBL-EC- and ESBL-KP-BSI, focus on cefepime exposure.	EC, KP
Panhotra BR ²⁰	2001-2003	Kingdom of Saudi Arabia	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors & clinical outcome of ESBL-KP-bacteraemia (hospital acquired)	KP
Marra AR ²¹	1996-2001	Brazil	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	ESBL-KP- associated mortality	KP
Skippen I ²²	2003-2005	UK	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Risk factors for & outcomes of ESBL-EC- and ESBL-KP-invasive transmission of organism in the healthcare setting	GNB
Schwaber MJ ²³	2000-2003	Israel	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality	Outcomes of ESBL-production in Enterobacteriaceae-bacteraemia.	GNB
Apisarnthanarak A ²⁴	2003-2004	Thailand	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	All adult patients	Entire hospital	All-cause mortality, LOS	Clinical & molecular epidemiologic factors associated with community onset ESBL-EC- infections, hospital resource utilisation, estimate costs associated with medical care (hospitalised patients)	EC
Umbarello M ²⁵	1999-2003	Italy	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS, ICU-LOS	Factors associated with isolation of ESBL- KP-strains	KP
Teistner R ¹¹	2008-2010	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital,	All-cause mortality, LOS	Difference in mortality: ESBL-EC-BSIs vs. non-ESBL-EC-BSIs, molecular epidemiology of ESBL-positive isolates	EC

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Apisarntharak A ²⁶	2003-2004	Thailand	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Risk factors for & outcomes of ESBL-EC- and ESBL-KP-infections (healthcare associated)	EC, KP
Kanafani ZA ²⁷	2003	Lebanon	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Epidemiology of infections with ESBL-EC and ESBL-Ks at AUBMC risk factors & outcomes of infections - focus on effect of prior antibiotic administration & the risks imparted by specific classes of antimicrobial agents	GNB
Zaoutis TE ²⁸	1999-2003	USA	Case cohort study	Non-ESBL-infection	Children	Entire hospital	All-cause mortality, LOS	Risk factors & outcomes associated with ESBL-EC-and ESBL-KP-BSI	EC, KP
Goh LC ²⁹	2003-2004	Malaysia	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Impact of ESBL-KP-respiratory tract infections on hospital mortality, requirement for mechanical ventilation & length stay	KP
Melzer M ³⁰	2003-2005	UK	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Differences in mortality & length of hospital stay & time from bacteraemia to death in patients with ESBL-EC- vs. non-ESBL-EC-bacteremic-infection	EC
Song KH ³¹	2000-2006	South Korea	Case cohort study	Non-ESBL-infection	Patients with spontaneous bacterial peritonitis	Not provided	All-cause mortality (28 day)	Outcomes of ESBL-EC-and ESBL-Ks- vs non-ESBL-EC-and ESBL-Ks-SBP (based on isolation from ascites), impact of ineffective initial antimicrobial therapy on outcome in patients with ESBL-EC- and ESBL-Ks-SBP, risk factors for infection by ESBL-producing microorganisms.	GNB
Bennett JW ³²	2004-2008	USA	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU, Surgical ward, Burn unit	All-cause mortality (28 day)	ESBL types and strain variability, presence of host factors to determine potential role in morbidity and mortality during ESBL-KP-infections	KP
Recarichi EM ³³	2000-2007	Italy	Cohort study, retrospective	Non-ESBL-infection	Patients with hematological malignancies	Entire hospital	All-cause mortality (28 day)	Risk factors for mortality in patients suffering from hematological malignancies with concurrent EC-bacteraemia. Focus on impact of ESBL- production & fluoroquinolone resistance by bacterial isolates	EC
Fuon FF ³⁴	2006-2009	Brazil	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day), LOS	Risk factors & mortality rate in ESBL-KP-bacteraemia	KP
Kang CI ³⁵	2008-2009	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Risk factors of ESBL-EC among community-onset bacteraemia, treatment outcomes	EC

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Pena C ³⁶	1996-2003	Spain	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Risk factors for mortality among patients with EC- infections	EC
Tumbarello M ³⁷	2006	Italy	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	ICU, Medical ward, Entire hospital, surgical wide	All-cause mortality (21 day), LOS	Clinical & economic impacts of ESBL production, inadequate Initial Antibiotic Therapy of EC-BSI	EC
Kang C ³⁸	2006-2009	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality (28 day)	Impact of ESBL-producing bacteraemia on outcome in patients with hematologic malignancy.	EC, KP
Wu YH ³⁹	2009-2012	Taiwan	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Medical ward	LOS	Host-related risk factors for community-onset UTI due to levofloxacin- or cefazolin-nonsusceptible isolates or uropathogens with ESBL production, clinical impact of UTIs due to antimicrobial-nonsusceptible pathogens	GNB
Rodriguez-Bano J ⁴⁰	2004-2006	Spain	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Epidemiology & risk factors (focus on previous antimicrobial use) & mortality rate for patients with ESBL-EC-COBSI	EC
Gürttnke S ⁴¹	2008-2011	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Distribution of ESBL genotypes, hospital mortality in cases of ESBL-KP-BSI	KP
Oh MM ⁴²	2006-2011	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients after Prostatitis Biopsy	Entire hospital	LOS	Impact of ESBL-positive-strains on clinical course & progression to chronic prostatitis in patients with postbiopsy acute prostatitis.	GNB
Leistner R ⁴³	2008-2011	Germany	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Financial disease burden attributable to ESBL-positive species in cases of EC-and KP-BSI	EC, KP
Lin JN ⁴²	2005-2009	Taiwan	Case cohort study	Non-ESBL-infection	All kinds of patients	Emergency Room	Attributable mortality, all-cause mortality (28 day), LOS, ICU-LOS	Clinical & microbiological characteristics, risk factors for acquisition of infection, prescription of initial empirical antibiotics mortality rate of infection	GNB
Ku NS ⁴⁴	2006-2010	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (28 day)	Clinical usefulness of breakpoints for treatment of Enterobacteriaceae-bacteraemia, (focus on EC- and Ks-bacteraemia): CLSI 2009- vs. CLSI 2010-guidelines.	EC, KP

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Anunnatsiri S ⁴⁵	2005-2006	Thailand	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Incidence of ESBL-EC-septicemia, factors associated with infection & clinical outcomes	EC
Kang CI ⁴⁶	1998-2002	South Korea	Case cohort study	Non-ESBL-infection	All kinds of patients	Hospital-wide	All-cause mortality (28 day)	Risk factors for mortality & treatment outcome of ESBL-EC- and ESBL-KP-BSI	EC, KP
Raviv Y ⁴⁷	2004-2007	Israel	Cohort study, retrospective	Control group: non-ESBL-infection, second control group: no infection	patients with lung transplantation	Not provided	All-cause mortality (28 day)	Outcomes of lung transplant recipients infected by CRKP and ESBL carbapenem-sensitive KP (referred to MDR-KP)	KP
Kim HJ ¹³	2005-2010	South Korea	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Medical ward	All-cause mortality (28 day), LOS	Clinical outcome of patients with biliary tract infection: ESBL-producing bacterial isolates vs. non-ESBL-producing-bacterial isolates, predictors of poor prognosis, impact of ineffective antimicrobial therapy on clinical outcome	EC, KP
MacVane SH ⁴⁸	2011-2012	USA	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality, LOS	clinical & economic outcomes of patients with ESBL-EC- and ESBL-KP-UTI vs. non-ESBL-EC- and non-ESBL-KP-UTI	EC, KP
Abhilash KP ⁴⁹	2007	India	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Prevalence & risk factors & outcome of antibiotic treatment among hospitalised patients with ESBL-EC- and ESBL-Ks-BSI	GNB
Rhantni M ⁵⁰	2006	India	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Prevalence & impact on clinical outcome of ESBL-production among nosocomial isolates of EC & KP	EC, KP
Han SB ⁵¹	2009-2013	South Korea	Cohort study, retrospective	Non-ESBL-infection	Children (immunocompromised, with cancer, neutropenic fever)	Pediatric ward	Attributable mortality, all-cause mortality (28 day)	Clinical outcomes of ESBL-EC- and ESBL-KP-bacteraemia & their antibiotic susceptibilities	EC, KP
Lee S ⁵²	2009-2011	South Korea	Cohort study, retrospective	Non-ESBL-infection	Patients with Acute Pyelonephritis	Entire hospital	All-cause mortality (14 day), LOS	Impact of ESBL on clinical outcomes of Acute Pyelonephritis treated with empirical ceftriaxone (which was inappropriate for ESBL-producing organisms)	EC
Artero A ⁷⁰	2013-2015	Spain	Cohort study, prospective	Non-ESBL-infection	Elderly	Medical ward	All-cause mortality, LOS	Identify clinical factors to predict ESBL-EC among elderly patients with UTI admitted to hospital in a high rate setting of ESBL-EC	EC

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Chen IL ⁷¹	2004-2015	Taiwan	Cohort study, retrospective	Non-ESBL-infection	Neonates	Neonatal ward	All-cause mortality	Compare the clinical characteristics & laboratory data of preterm babies with EC BSI: survival vs. nonsurvival groups, ESBL vs non-ESBL groups, determine the predictive factors of EC BSI in preterm babies	EC
Islas-Munoz B ⁷²	2016-2017	Mexico	Cohort study, prospective	Non-ESBL-infection	Cancer patients	Oncologic ward	All-cause mortality (28 day)	Evaluate the clinical epidemiological characteristics & risk factors associated with mortality in cancer patients with BSI-special emphasis on MDR bacteria	GNB (and others)
Ma J ⁷³	2012-2015		Cohort study, retrospective	Non-ESBL-infection	Patients with hematological diseases	Entire hospital	All-cause mortality (28 day)	Evaluate the antimicrobial resistance & clinical features & risk factors for septic shock & death of nosocomial EC-BSI	EC
Man MY ⁷⁴	2009-2016	China	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients, except patients from Burn unit, transplant surgery ward or with thoracic therapy	Entire hospital	All-cause mortality (28 day)	Evaluate the incidence & clinical characteristics & outcomes of patients with KP BSI in critical care & general ward settings	KP
Marando R ⁷⁵	2016	Tanzania	Cohort study, prospective	Non-ESBL-infection	Neonates	NICU	All-cause mortality	Investigate factors associated with ESBL-PE neonatal sepsis & mortality among neonates, characterise selected isolates to show virulence potential & transmission dynamics	GNB
Namikawa H ⁷⁶	2011-2015	Japan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Investigate clinical characteristics of patients with ESBL-EC-BSI	EC
Shi SH ⁷⁷	2008-2015	China	Cohort study, retrospective	Non-ESBL-infection	Patients with pyogenic liver abscess	Centre for hepatopancreaticobiliary diseases	All-cause mortality, LOS	Aetiology & morbidity & clinical characteristics of pyogenic liver abscess caused by ESBL-PE	GN
Tanir Basaranoglu S ⁷⁸	2011-2015	Turkey	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality (28 day)	Assess risk factors for health care associated ESBL-KP-BSI in children, analyze clinical outcomes: ESBL-KP vs. non-ESBL-KP	KP
Bazazi K ⁷⁹	2009-2015	France	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality, LOS, ICU-LOS	Determine, among ESBL-PE carriers, the prevalence & associated factors & clinical impact of ESBL-PE pneumonia, determine factors associated with ICUAP caused by carbapenem-resistant bacteria	GNB

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Ray S ⁸⁰	2014-2016	India	Cohort study, prospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Investigate spectrum of microbial resistance pattern in the community and their effects on mortality	GNB
Haruki Y ⁸¹	2006-2016	Japan	Cohort study, retrospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Compare the clinical characteristics & outcomes of critically ill patients in an ICU, who were hospitalised for BSI caused by ESBL-EC or non-ESBL-EC.	GNB
Lin WT ⁸²	2009-2014	Taiwan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Investigate the clinical manifestations & bacteriological features of culture-proven, GNB arthritis	GNB
Guys H ⁸³	2006-2011	South Africa	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality	Describe the clinical presentation of KPBSI, risk factors associated with ESBL-KPBSI, antibiotic susceptibility patterns of the KP isolates & KPBSI mortality including factors associated with in-patient mortality	KP
Lee CC ⁸⁴	2008-2013	Taiwan	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Emergency Department	Attributable mortality, all-cause mortality (28 day), LOS, ICU-LOS	Analyse the impact of ESBL-producing isolates on the outcome of bacteremic patient after controlling for baseline patient characteristics & bacteraemia severity by using a propensity-matched analysis (PSM)	GNB
Huang YY ⁸⁵	2011-2013	Canada	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Determine cumulative incidence of ESBL urosepsis, identify major risk factors for ESBL urosepsis, determine impact of international travel on development of ESBL urosepsis	EC, KP
Komatsu Y ⁸⁶	2008-2013	Japan	Case cohort study	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality (14 day)	Identify risk factors & clinical outcomes in patients with BSI due to ESBL- or carbapenemase-producing EC, determine prevalence & genetic background	EC
Liu MM ⁸⁷	2011-2016	China	Case cohort study	Control group: non-ESBL-infection, second control group: no infection	ICU-patients	ICU	All-cause mortality	Identify risk factors for ESBL-producing ECBSI among carriers at ICU	EC
Nivesvivat T ⁸⁸	2010-2017	Thailand	Cohort study, retrospective	Non-ESBL-infection	Children	Pediatric ward	All-cause mortality, LOS	Determine prevalence, risk factors & clinical outcomes of ESBL-producing EB in paediatric BSI	EC, KP

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	Years	Country	Study design	Control group	Study population	Setting	Outcome definition	Main objective	Pathogen
Cordery RJ ⁸⁹	2004-2006	UK	Cohort study, retrospective	Non-ESBL-infection	ICU-patients	ICU	All-cause mortality	Elucidate specific risk factors for the acquisition of ESBL infection in the ICU; all-cause mortality (in ICU) compared in patients with infections due to ESBL- and non-ESBL-producing organisms	GNB
Paikos GL ⁹⁰	2003-2005	Greece	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Identify risk factors associated BSI caused by integron-carrying EB; evaluate the consequences of these genetic elements on patient outcome	GNB
Gudiol C ⁹¹	2006-2008	Spain	Cohort study, prospective	Non-ESBL-infection	Cancer patients and hematopoietic stem cell transplant patients	Entire hospital	All-cause mortality	Assess clinical features, risk factors, molecular epidemiology & outcome of ESBLEC BSI in hospitalised cancer patients	EC
Marchaim D ⁹²	2006-2008	Israel	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality, LOS	Define predictors & outcomes of ESBL BSI among patients with bacteraemia due to EB upon hospital admission	GNB
Menashe G ⁹³	1997	Israel	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Determine: prevalence of ESBL-P organisms among adult patients with nosocomial EB BSI treated in our institution; association between ESBL production & resistance to other antibiotics; clinical characteristics of patients with nosocomial ESBL-P BSI compared with those infected with non-producing strains; impact of ESBL production on outcome of patients with nosocomial EB BSI	GNB
Ortega M ⁹⁴	1991-2007	Spain	Cohort study, prospective	Non-ESBL-infection	All kinds of patients	Entire hospital	All-cause mortality	Describe source, resistance rate to fluoroquinolone & beta-lactam antibiotics and mortality of EC BSI episodes in a single institution; identify predictive factors for isolation of fluoroquinolone-resistant or ESBL- producing strains.	EC
Sziglyi M ⁹⁵	2005-2008	Hungary	Cohort study, retrospective	Non-ESBL-infection	All kinds of patients	Entire hospital	Attributable mortality, all-cause mortality,	Investigate risk factors for & outcomes of BSI caused by ESBL-producing and ESBL-non-producing KP	KP
Tsai SS ⁹⁶	2005-2006	Taiwan	Cohort study, retrospective	Non-ESBL-infection	Diabetic patients	Entire hospital	All-cause mortality	Analyze characteristics, risk factors & outcomes of diabetic patients with community- vs. hospital-acquired KP BSI	KP

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3 EC = *Escherichia coli*
4 KP = *Klebsiella pneumoniae*
5 GNB = Gram-negative bacteria
6 BSI = Bloodstream infection
7 UTI = Urinary tract infection
8 ICU = Intensive care unit
9 NICU = Neonatal intensive care unit
10 ESBL-PE = Extended-spectrum beta-lactamase-producing Enterobacteriaceae
11 EB = Enterobacteriaceae
12 LOS = Length of stay
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Supplementary table S5: Risk of bias assessment of case cohort studies according to Newcastle - Ottawa quality assessment scale:

Assessment criteria / Study author	1. Is the case definition adequate?	2. Representativeness of the cases:	3. Selection of Controls	4. Definition of Controls	5. Comparability of cases and controls on the basis of the design or analysis	6. Ascertainment of exposure	7. Same method of ascertainment for cases and controls	8. Non-Response rate
Lautenbach, E.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Apisarntharak, A.	Green	Green	Yellow	Green	Green	Green	Green	Green
Briongos-Figuero, L-S.	Green	Green	Yellow	Yellow	Grey	Green	Green	Green
Stone, P.W.	Green	Green	Brown	Yellow	Grey	Green	Green	Green
Kola, A.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Tsai, M.H.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Maslikowska, J.A.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Nguyen, M. L.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Denis, B.	Green	Green	Yellow	Green	Yellow	Green	Green	Green
Chopra, T.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Skippen, I.	Green	Green	Yellow	Yellow	Yellow	Green	Grey	Green
Apisarntharak, A.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Tumbarello, M.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Apisarntharak, A.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Kanafani, Z. A.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Zaoutis, T. E.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Song, K. H.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Kang, C. I.	Green	Green	Yellow	Yellow	Grey	Green	Green	Green
Rodriguez-Bano, J.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Lin, J. N.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Ku, N. S.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Kang, C. I.	Green	Green	Yellow	Yellow	Green	Green	Green	Green
Huang, Y. Y.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Komatsu, Y.	Green	Green	Yellow	Yellow	Yellow	Green	Green	Green
Liu, M. M.	Green	Green	Yellow	Green	Yellow	Green	Green	Green

Risk of bias assessment of cohort studies according to Newcastle - Ottawa quality assessment scale:

Study author / Assessment criteria	1. Representativeness of exposed cohort	2. Selection of non-exposed cohort	3. Ascertainment of exposure	4. Demonstration that outcome of interest not present at start	5. Comparability based on design or analysis	6. Assessment of outcome	7. Follow-up long enough for outcome	8. Adequacy of follow up of cohorts
Jean, S.S.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
Bhavnani, S. M.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Blomberg, B.	Yellow	Green	Green	Green	Grey	Yellow	Green	Green
Pena, C.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Onken, A.	Green	Green	Green	Green	Grey	Yellow	Green	Green
Melzer, M.	Green	Green	Green	Green	Grey	Yellow	Green	Green
Bennet, J.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Wu, Y.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Abhilash, K.	Green	Green	Green	Green	Green	Yellow	Yellow	Green
Artero, A.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Islas-Munos, B.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Marando, R.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Razazi, K.	Green	Green	Green	Green	Green	Yellow	Green	Green
Ray, S.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Panhotra, B.	Green	Green	Green	Green	Green	Yellow	Green	Green
Kim, S.	Green	Green	Green	Green	Green	Yellow	Green	Green
Chayakulkeeree, M.	Green	Green	Green	Green	Green	Yellow	Green	Green
Apisarnthanarak, A.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
Ha, Y.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Du, B	Green	Green	Green	Green	Green	Yellow	Green	Green
Pillay, T.	Yellow	Green	Green	Green	Grey	Yellow	Green	Green
Kim, B.	Green	Green	Green	Green	Green	Yellow	Green	Green
Kim, Y	Green	Green	Green	Green	Green	Yellow	Green	Green
Marra, A.	Green	Green	Green	Green	Green	Yellow	Green	Green
Schwaber, M.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
Leistner, R.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
Loh, L.C.	Green	Green	Green	Green	Green	Yellow	Green	Red
Trecarichi, E.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
Tuon, F.	Green	Green	Green	Green	Green	Yellow	Green	Green
Kang, C. I.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
Pena, C.	Green	Green	Green	Green	Grey	Yellow	Green	Green
Tumbarello, M.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
Gurntke, S.	Green	Green	Green	Green	Green	Yellow	Green	Green
Oh, M.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
Leistner, R.	Green	Green	Green	Green	Grey	Yellow	Green	Green
Anunnatsiri	Yellow	Green	Green	Green	Green	Yellow	Green	Green

1	Raviv, Y.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
2	Kim, H.J.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
3	MacVane, S.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
4	Shanthi	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
5	Han, S.B.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
6	Han, S.B.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
7	Lee, S.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
8	Chen, I-L.	Green	Green	Green	Green	Yellow	Yellow	Green	Green
9	Ma, J.	Green	Green	Green	Green	Green	Yellow	Green	Green
10	Ma, J.	Green	Green	Green	Green	Green	Yellow	Green	Green
11	Man, M.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
12	Namikawa, H.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
13	Namikawa, H.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
14	Shi, S.	Yellow	Green	Green	Green	Grey	Yellow	Green	Green
15	Tanir Basarangolu, S.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
16	Tanir Basarangolu, S.	Yellow	Green	Green	Green	Yellow	Yellow	Green	Green
17	Haruki, Y.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
18	Lin, W.	Green	Green	Green	Green	Grey	Yellow	Green	Green
19	Lin, W.	Green	Green	Green	Green	Green	Yellow	Green	Green
20	Buys, H.	Green	Green	Green	Green	Green	Yellow	Green	Green
21	Lee, C.C.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
22	Lee, C.C.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
23	Nivesvivat, T.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
24	Nivesvivat, T.	Yellow	Green	Green	Green	Green	Yellow	Green	Green
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Supplementary table S6: Source of heterogeneity among effect estimates in studies on ESBL bloodstream infections in comparison with patients with non-ESBL bloodstream infections assessed using univariate meta-regression:

Subgroups / Outcome	All-cause mortality	Length of Stay
Mortality time	0.85	-
Pathogen	0.45	0.34
Study design	0.51	0.21
Study country	0.22	0.09
Income classification	0.17	0.80
Study period	0.57	0.78
Study setting: ICU ward	0.78	0.97
Study setting: Neonatal ward	0.62	0.97
Study setting: Pediatric ward	0.96	0.96
Study population: ICU patients	1.00	-
Study population: Children	0.96	0.96
Study population: Neonates	0.62	0.97
Information about therapy	0.53	
Appropriateness of therapy reported	0.68	
Information about outcome of therapy	0.74	-
MIC reported	0.28	-



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5,6



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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	suppl.material
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8 and suppl. material
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	suppl.material
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8 and suppl. material
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7,8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11



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